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To Mum, Dad & Colum.
I don’t understand these people

Saying the hill’s too steep

Well they talk and talk forever but they just never climb

Star Star
The Frames
# Table of Contents

**THESIS ABSTRACT**  
3

**DECLARATION OF ORIGINALITY**  
4

**EXECUTIVE SUMMARY**  
6

**SUMMARY INTRODUCTION**  
11

**CHAPTER 1 – LITERATURE REVIEW**  
19

A review of the differences and similarities between generic drugs and their originator counterparts, including economic benefits associated with usage of generic medicines, using Ireland as a case study.

**CHAPTER 2**  
93

Critical appraisal of the literature on stakeholder perceptions of generic medicines — a systematic review.

**CHAPTER 3**  
156

Perceptions of generic medicines amongst general practitioners, community pharmacists and patients in Ireland.

**CHAPTER 4**  
208

Physician and community pharmacist perceptions of generic medicines: what they think and how they differ.

**CHAPTER 5**  
237

Beliefs, perceptions, and behaviours of general practitioners towards generic medicines.

**CHAPTER 6**  
265

Perceptions and attitudes of community pharmacists regarding generic medicines: a mixed methods study.

**CHAPTER 7**  
295

Patient perceptions of generic medicines: a mixed-methods study.

**CHAPTER 8**  
325

A method for the design and development of medical or health care information websites to optimize search engine results page rankings on Google.  
Addendum 1 to Chapter 8  
Addendum 2 to Chapter 8

**CHAPTER 9**  
378

Generic medicines: an evaluation of the accuracy and accessibility of information available on the Internet.

**CHAPTER 10**  
419

What answers does the Internet provide for Irish patients with questions about generic medicines?

**SUMMARY CONCLUSION**  
444

**ACKNOWLEDGEMENTS**  
447
APPENDICES

APPENDIX 1
ETHICS APPROVAL FOR THE STUDIES IN CHAPTERS 2 TO 7.

APPENDIX 2
CHAPTERS, AS PUBLISHED.

APPENDIX 3
ADDITIONAL PAPERS PUBLISHED, IN PARALLEL WITH THIS THESIS, WHILE REGISTERED FOR THIS DEGREE.
Thesis Abstract


Background: Generic medicines result from expired intellectual property protection and the ability of pharmaceutical producers, other than originator companies, to manufacture analogous medicines containing identical active ingredients and to distribute them in relevant markets. Cost reductions associated with procurement of generics by national agencies, and subsequent savings for patients buying generic medicines from pharmacies, result in policies regarding generic medicines and reference pricing being promoted by governments internationally. In Ireland, however, generic medicines usage has been poor historically and attitudes of stakeholders, other than the Irish Government, have been relatively negative. In June 2013 the Health (Pricing and Supply of Medical Goods) Act was signed into law, meaning that Irish patients are now more likely than ever before to receive a generic medicine.

Objectives From 2013, general practitioners (GPs) and pharmacists alike are likely to encounter greater patient awareness, and discussion, of generic medicines, their potential benefits and disadvantages. This thesis focused initially on providing a comprehensive description of generic medicines and their development and, at a time immediately preceding introduction of the Irish Act, on gaining insight into current stakeholder attitudes and awareness towards generic medicines in Ireland. In parallel, a novel tool based on principles of understandability and readability of text was developed. This was utilised to assess websites most likely to be accessed by patients seeking information regarding generic medicines across a number of English speaking regions, with emphasis on Ireland.

Methods Mixed methods studies (in the format of 1:1 interviews) with GPs, pharmacists and patients from rural and urban settings in Ireland. Analysis of interviews was both qualitative and quantitative using SPSS (version 20) and NVivo (version 9), as appropriate. Evaluation of websites was completed with a novel Website Quality Assessment (WQA) tool, developed as part of this thesis. Websites most likely to be used by searchers looking for online information about generic medicines in five English-speaking geographical regions (US, UK, Ireland, Canada and Australia) were assessed for quality and accessibility (in terms of readability and understandability) of information provided.

Results Analysis of survey data showed that there was a hierarchy of understanding and acceptance of generic medicines in Ireland. In summary, pharmacists had the greatest understanding of generic medicines and the processes associated with their regulation and safety, followed by GPs and then patients. Notably, GPs had less confidence in generics than pharmacists; indeed 5/34 (15%) of GPs would prefer not to use a generic medicine if provided an originator alternative versus 3/44 (7%) of pharmacists. Patients expressed the lowest level of confidence with 9/38 (24%) stating a preference for the branded medication in addition to a belief that generics were of poorer quality than originator medicines.

Use of the WQA tool, following peer review and validation of its design, demonstrated clearly that readability and understandability of healthcare information influenced the Google search ranking of generic medicine-related websites. In Ireland, analogous to other jurisdictions, none of the websites most likely to be seen by a searcher demonstrated the desired combination of scoring highly for both quality of information and readability.

Conclusions: In summary, these investigations impart new insights regarding knowledge, attitudes and behaviours in Ireland towards generic medicines, determine and evaluate the Internet resources likely to be accessed by those seeking knowledge on this topic across a number of English-speaking regions, and provide a unique tool to enhance the promotion and provision of relevant information.
Declaration of Originality
Declaration of Originality

I, Suzanne Dunne, declare that the work contained in this thesis is original and, excepting where stated in the following chapters, all work was completed by me.

[Signature]
Executive Summary
Executive Summary

Generic medicines are those medicines that are manufactured following expiration of patent protection, or other marketing exclusivities, which were afforded to a proprietary pharmaceutical product. Generic medicines are generally lower in price than the proprietary drug and, hence, use of generics is associated with significant cost savings in many healthcare systems worldwide - without any negative clinical impact on patient care. In Ireland, however, usage of generic medicines has been low historically and, as a result, the Irish Government has recognised this as an area in which potential cost savings may be made. To this end, the Health (Pricing and Supply of Medical Goods) Act 2013 was signed into law, in Ireland, in June 2013. This legislation enables reference pricing and generic substitution for the first time in this market. (A review of the background to this thesis, which was published in *BMC Pharmacology & Toxicology*, can be seen in Chapter 1).

The knowledge gaps that this thesis aims to bridge are: 1) the lack of information regarding Irish stakeholders' opinions towards generic medicines, and 2) the role of the Internet in providing Irish and international healthcare consumers with information about generic medicines.

Hence, the objectives of this thesis were twofold: firstly, to determine the perceptions of, and behaviours towards, generic medicines among the principal stakeholder groups in Ireland (prescribers, dispensers and consumers) and, from this, to elucidate what potential challenges may be faced during the introduction of the new legislation. Moreover, as the implementation of generic substitution and reference pricing means that Irish patients are now more likely than ever before to receive a generic drug, and given that the first port of call for many people looking for healthcare/medical information in the 21st century is the
Internet; the second objective of this research was to assess the quality and accessibility (in terms of readability and understandability) of online information relevant to generic medicines.

To investigate the perceptions, beliefs and behaviours towards generic medicines in Ireland, one-to-one semi-structured interviews were conducted. These were undertaken with members of each of the three stakeholder groups specifically, 1) general practitioners (GPs) as representatives of prescribing physicians, 2) pharmacists, as dispensers of medicines and 3) patients, as consumers of medicines. The aim of these interviews was to elucidate the opinions and perceptions of these stakeholders, with regard to generic medicines, in the time period leading up to the introduction of the new legislation. Both qualitative and quantitative assessments were undertaken. Qualitative analysis for themes emerging from the interviews was completed using NVivo (version 9). Approval of the design and conducting of these studies was granted by the Ethics Committee of the Irish College of General Practitioners (ICGP).

These interviews determined that there was a hierarchy of understanding amongst stakeholders, with pharmacists demonstrating the greatest understanding, the most positive views and the most acceptance of generic medicines (Chapters 3, 4 and 6). By comparison, while GPs tend to hold mainly positive views, they exhibited some reticence regarding generics, and potential exists for this to influence patient perceptions (Chapters 3, 4 and 5). Indeed, patients held the most negative opinions of the three groups, expressing distrust in generic medicines and a strong preference for branded (i.e., proprietary) medications (Chapters 2 and 7).

Furthermore, insights gained early in the interview process showed that provision of information and education of stakeholders was a recurring theme. Hence, a
novel tool was developed for use in the design and developing of websites to provide medical/healthcare information, and the paper describing this tool has been published in the leading peer-reviewed journal on medical Internet research (Chapter 8). It was then used to assess existing websites that provide information on generic medicines (and which were those most likely to be looked at by a patient performing an Internet search in the US, Canada, Ireland, the UK and Australia). The results of this work, focusing particularly on the quality and accessibility of the information (in terms of readability and understandability) targeting the general public have also been published in *BMC Medical Informatics and Decision Making* (Chapter 9). Additionally, an analysis of the online information in an exclusively Irish context has also been published (Chapter 10). More specifically, it was determined that while none of the websites likely to be looked at by searchers provided inaccurate information about generic medicines *per se*, the information given was lacking in most cases. Moreover, it appeared that relatively poor attention to detail pertained regarding syntax and language used, that is, ensuring that the information provided was written in a manner that was easily read and understood by most members of the public. In addition, none of the websites proved both accurate (that is, quality of information) and readable (and hence understandable) (Chapters 9 and 10).

Future work deriving from this thesis may focus on the utilisation of the data collected during the interviews studies, as they provide a unique baseline for comparative investigations assessing changing perceptions of stakeholders towards generic medicines in the future, particularly in the context of determining the impact of the new Health (Pricing and Supply of Medical Goods) Act. Additionally, in the context of online healthcare information provision,
opportunities may exist to exploit the WQA tool by partnering with those designing healthcare/medical information websites.

In conclusion, this research fills a knowledge gap in that it is the first series of studies of the perceptions of pharmacists and patients in Ireland towards generic medicines. Additionally, it is the first study of GP opinions on this topic performed in Ireland since 1997. The results provide unique and singular insight into the opinions of key stakeholders in the advent of a major change in Irish healthcare policy and may, therefore, represent the baseline for future study of these views post-implementation of these changes. Moreover, in the context of modern information provision, while assessing current generic medicines-related websites as part of this thesis, clear deficiencies in quality of information and accessibility of text were observed. As a consequence of this thesis, those working to eradicate these deficiencies when designing healthcare/medical information provision websites may now utilise the innovative and sophisticated (yet user-friendly) tool developed and validated as part of my work.

In summary, therefore, this thesis reports new insights regarding knowledge, attitudes and behaviours towards generic medicines in Ireland, determines and evaluates the internet resources likely to be accessed by those seeking knowledge on this topic across a number of English-speaking regions, and provides a novel tool to enhance the promotion and provision of relevant information.
Summary Introduction
Summary Introduction

Personal Interest

Having worked in the pharmaceutical manufacturing industry for nearly a decade and a half, following gaining my B.Sc. (Hons) and M. Sc. degrees, I became intrigued by the difference between proprietary or “brand name” drugs and those manufactured under the label of “generic” medicines. During my career, I have been involved in the manufacture of both brand name and generic medicines, and could see that, in the case of generics, certain markets appeared to order more than others. This got me wondering about why certain countries made more use of generic drugs, and what the situation was with regard to use of generic drugs in Ireland. When I looked into the Irish situation, information from the European Generics Association showed me that Ireland was at the bottom of the “league table” in terms of the usage of generic medicines - but didn't give any indication as to why this was the case.

On a personal level, I had, for many years, held the ambition to complete a PhD and as I found myself wondering about this topic and asking questions like: What are the attitudes to generic medicines within different stakeholder groups In Ireland? What are the main differences between generic and proprietary drugs? And what is the type and quality of information available to people regarding generic medicines? I began to ask if this could make a project suitable for a PhD. A bit more thought, structure, investigation and two agreeable PhD supervisors later, these vague wonderings had coalesced into what eventually became this PhD research project.
Background

Generic medicines are those that are made, following expiration of patent(s) and other exclusivity arrangements, and which are generally marketed using the International Non-Proprietary Name (INN) of the active drug. Generic drugs may be manufactured by companies other than that which produced the proprietary product, although in many cases the proprietary manufacturer may also produce a generic version of their product.

Ireland has, historically, had a poor track record of usage of generic medicines, being amongst the lowest in the EU. As significant cost savings are associated with usage of generic medicines, legislation to introduce generic substitution and reference pricing in Ireland was originally mooted by the Irish Government in 2010, and was eventually signed into law, in June 2013, as The Health (Pricing and Supply of Medical Goods) Act 2013 (http://www.irishstatutebook.ie/2013/en/act/pub/0014/index.html). This legislation introduces the legal basis for reference pricing and generic substitution in Ireland, for the first time. However, no comprehensive scientific investigation into the reasons for Ireland’s low usage of generics has been completed. Moreover, in an era when the landscape of medicines provision in Ireland is undergoing significant change, having an understanding of reasons behind the reticence of the key stakeholders in this process to use generics may help to understand the challenges which may be faced during the introduction of the new legislation and may also provide essential information to ensure successful acceptance of increased usage of generic medicines in Ireland.

The primary research question in this PhD thesis was, therefore: what are the perceptions held by key stakeholders of generic medicines and how might these
opinions affect the success or otherwise of the changes proposed in the Irish healthcare system?

To investigate this, semi-structured interviews were undertaken with three stakeholder groups: 1) general practitioners - as representatives of prescribing physicians, 2) pharmacists – as dispensers of medicines, and 3) patients – as medicines consumers. Four publications have been prepared from this work, represented in this thesis as chapters 4 to 7.

The changes that are ongoing in the Irish healthcare system, specifically the introduction of reference pricing and generic substitution, mean that those in the patient cohort are more likely than ever before to receive a generic medicine. Given the opinions expressed in the studies undertaken in this project, and also as the Internet is now one of the first ports of call for most people seeking medical or healthcare information, further investigations were performed into the quality and accessibility of information on generic medicines provided on the Internet. This work involved the developing of a novel tool to assess healthcare information-providing websites, which was then used to assess the information provided, on generic medicines, internationally. This work is represented in this thesis in chapters 8 to 10, inclusive.

This thesis tackles research questions in two main areas – perceptions of Irish stakeholders regarding generic medicines, completed as a holistic assessment of stakeholder opinions and behaviours and the quality and availability of online information available to patients. It furthermore provides a novel (peer-reviewed and published) tool, which may be used in the design of healthcare/medical information websites. A holistic oversight of all of the information generated in
this body of work not only elucidates the opinions of Irish stakeholders towards
generic medicines, thereby allowing solutions to potential hurdles to be sought in
relation to improving Ireland’s use of generic drugs, but also provides tools to
enable one of the primary solutions to the challenges described, namely the
provision of clear, understandable and accessible information to educate all
stakeholders.

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Thesis Layout

The “work chapters” of this thesis are laid out as follows:

The interview studies (representing four of the seven ‘work’ chapters in this thesis) consisted of three distinct and separate fieldwork endeavours – one for each of the stakeholder groups. While the methodological approach taken in each was similar, they varied considerably with respect to location chosen for the recruitment of participants, the number of participants interviewed and the specific timings for engagement with study groups. Distinct study instruments were used for each of the three studies.

Each endeavour resulted in one distinct paper and the fourth paper is a comparison of the pertinent points in the cases of the two healthcare professional studies only (that is, one paper across two studies that is novel in, for the first time, evaluating the similarities and differences of professional groups in Ireland).

The fourth study (that is, the medical informatics study) resulted in three papers.

Chapter 1 is a published review of the background to the subject area covered in this thesis. Entitled: A review of the differences and similarities between generic drugs and their originator counterparts, including economic benefits associated with usage of generic medicines, using Ireland as a case study, this article was published in BMC Pharmacology & Toxicology (unofficial impact factor: 3.15).
Chapter 2 is a systematic review and critical appraisal of the literature on stakeholder perceptions of generic medicines.

Chapter 3 is entitled *Perceptions of Generic Medicines Amongst General Practitioners, Community Pharmacists and Patients in Ireland* and represents all three of the interview studies collated into a single mixed-methods research chapter.

Chapter 4 is a comparison of the views of healthcare professionals which has been published by *Health Policy* (impact factor 1.550) with the title: *Physician and pharmacist perceptions of generic medicines: what they think and how they differ.*

Chapter 5 details the opinions of GPs and has been published in *Family Practice* (impact factor 1.828) as a paper entitled: *Beliefs, perceptions, and behaviours of general practitioners towards generic medicines.*

Chapter 6 describes the views of community pharmacists and has been published in *Journal of Managed Care & Speciality Pharmacy* (impact factor 2.41) as an paper entitled: *Perceptions and attitudes of pharmacists regarding generic medicines: a mixed methods study.*

Chapter 7: The views of the patient cohort have been described in a paper entitled: *Patient perceptions of generic medicines: a mixed-methods study.* This was published in *The Patient* (impact factor 1.565) on 03 Jan 2014.
Chapter 8 details the development and validation of the WQA tool. *A Method for the Design and Development of Medical or Health Care Information Websites to Optimize Search Engine Results Page Rankings on Google* was published in the *Journal of Medical Internet Research* (impact factor 4.7) on 27 Aug 13.

Chapter 9: Use of the WQA tool to evaluate online information most likely to be accessed by those in the patient cohort has been detailed in: *Generic medicines: an evaluation of the accuracy and accessibility of information available on the Internet.*

*BMC Medical Informatics and Decision Making* (impact factor 1.6) published this paper on 07 October 2013.

Chapter 10 represents an analysis of what Irish patients searching for online information about generic medicines might find and has been published by the *Journal of Generic Medicines* as a paper entitled: *What answers does the Internet provide for Irish patients with questions about generic medicines?*
Chapter 1 – Literature Review

A review of the differences and similarities between generic drugs and their originator counterparts, including economic benefits associated with usage of generic medicines, using Ireland as a case study.

Published in BMC Pharmacology & Toxicology on 05 Jan 13.

Citation:


This open access paper has been highly viewed and as a result has received a “Highly Accessed” designation from the journal. This identifies those articles that have been especially highly accessed relative to their age and the journal in which they were published.

Altmetric statistics (http://www.altmetric.com/details.php?citation_id=1157967) for this paper show that it ranks (at the time of preparation of this thesis) as the most highly accessed article online compared to all articles published by BMC Pharmacology and Toxicology.
A review of the differences and similarities between generic drugs and their originator counterparts, including economic benefits associated with usage of generic medicines, using Ireland as a case study.

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Abstract

Generic medicines are those where patent protection has expired, and which may be produced by manufacturers other than the innovator company. Use of generic medicines has been increasing in recent years, primarily as a cost saving measure in healthcare provision. Generic medicines are typically 20 to 90% cheaper than originator equivalents. Our objective is to provide a high-level description of what generic medicines are and how they differ, at a regulatory and legislative level, from originator medicines. We describe the current and historical regulation of medicines in the world’s two main pharmaceutical markets, in addition to the similarities, as well as the differences, between generics and their originator equivalents including the reasons for the cost differences seen between originator and generic medicines. Ireland is currently poised to introduce generic substitution and reference pricing. This article refers to this situation as an exemplar of a national system on the cusp of significant health policy change, and specifically details Ireland’s history with usage of generic medicines and how the proposed changes could affect healthcare provision.

Keywords

Generic, medicine, drug, pharmaceutical, biosimilar, prescribing, healthcare, economics, Ireland.
Review

Summary Introduction: What are Generic Medicines?

Generic medicines are those where the original patent has expired and which may now be produced by manufacturers other than the original innovator (patent-holding) company. The term “generic drug” or “generic medicine” can have varying definitions in different markets, however the term is commonly understood, as defined by the World Health Organisation (WHO), to mean a pharmaceutical product which:

- is usually intended to be interchangeable with an innovator product,
- is manufactured without a licence from the innovator company, and
- is marketed after the expiry date of the patent or other exclusive rights [1].

There are differing legal requirements in different jurisdictions that define the specifics of what a generic medicine is. However, one of the main principles underpinning the safe and effective use of generic medicines is the concept of bioequivalence.

Bioequivalence (BE) has been defined as follows: two pharmaceutical products are bioequivalent if they are pharmaceutically equivalent and their bioavailabilities (rate and extent of availability) after administration in the same molar dose are similar to such a degree that their effects, with respect to both efficacy and safety, can be expected to be essentially the same. Pharmaceutical equivalence implies the same amount of the same active substance(s), in the same dosage form, for the same route of administration and meeting the same or comparable standards [2].
The purpose of establishing bioequivalence is to demonstrate equivalence between the generic medicine and the originator medicine in order to allow bridging of the pre-clinical and clinical testing performed on the originator drug.

The objective of this article is to provide an accessible resource describing the foundation of generic medicines, from their legal advent in the mid 1980’s to how current legislation and regulation of generics affects, *inter alia*, their composition, regulatory approval, pricing, and ultimately acceptance by healthcare professionals and patients. In this paper, we also focus on Ireland’s emerging policy on generic medicine use. Ireland is one of the EU ‘bail-out’ countries, and is attempting to conserve resources given the prevailing economic climate. Ireland is, therefore, currently poised to make the legislative changes necessary to introduce generic substitution and reference pricing in order to achieve reductions in the medicines bill for the state (by promoting competition between suppliers of interchangeable medicines) and to ensure value for money in the supply of medicines and other items prescribed to patients. This article refers this situation as an exemplar of a national system on the cusp of significant medical policy change, and specifically details Ireland’s history with usage of generic medicines and how the proposed changes could affect healthcare provision.
Brief Comparison of Generic Medicines in the United States and Europe

Generic Medicines in the United States of America

The US Food and Drug Administration [FDA], which regulates the pharmaceutical market in the United States [3] defines generic medicines as:

- a drug product that is comparable to brand/reference listed drug product in dosage form, strength, route of administration, quality and performance characteristics, and intended use [4]

- copies of brand-name drugs and are the same as those brand name drugs in dosage form, safety, strength, route of administration, quality, performance characteristics and intended use [5].

The 1984 Drug Price Competition and Patent Term Restoration Act (more commonly known as the Hatch-Waxman Act) in the US allowed for an abbreviated system for approval of generic copies of all drugs approved after 1962 [4], meaning that pre-clinical and clinical testing did not have to be repeated for generics [6]. The intended result of this legislation was to ensure that generic medicines would be less expensive than the equivalent originator medicine because it was not necessary for generic medicine manufacturers to repeat discovery, pre-clinical and clinical studies [7, 8]. (It should be noted, as will be discussed later, that the cost of generics may vary considerably across countries depending on the specific active molecule involved, such that savings may not necessarily always accrue [9]). See Figure 1: Originator (NDA) versus Generic (ANDA) Review Process Requirements [8] for a comparison of the originator versus generic medicine review process.
To gain FDA approval, a generic medicine must:

- Contain the same active ingredient as the originator medicine (inactive ingredients may vary)
- be identical in strength, dosage form, and route of administration
- have the same use indications
- be bioequivalent
- meet the same batch requirements for identity, strength, purity, and quality
- be manufactured under the same strict standards of FDA’s good manufacturing practice regulations required for originator products [10].

The FDA’s formal definition of bioequivalence (BE) is: *the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study* [11].

Currently, FDA recommendations for bioequivalence comparisons, for medicines with an oral administration route, recommended use of (1) a criterion to allow the comparison, (2) a confidence interval for the criterion, and (3) a BE limit. Comparison criteria are represented by the blood plasma AUC (area under the curve) where the generic must demonstrate 80-125% of the bioavailability of the originator drug [11]. Other required measurements include the plasma concentrations and time points – such as $C_{\text{max}}$ (maximum concentration in plasma), $C_{\text{min}}$ (concentration at end of the dosing interval) and $C_{\text{av}}$ (average concentration over the dosing interval). The FDA’s BE guidance document recommends that
logarithmic transformation be provided for all measures and that the confidence interval (CI) values not be rounded off and therefore to pass a CI limit of 80-125% the value would have to be at least 80.00 and not more than 125.00 [11].

In the US, the limit of 80-125% is unchanged for Narrow Therapeutic Range [NTR] drugs [11].

In other countries this is not the always case. In Australia, for example, there are no generic versions of digoxin or phenytoin [both having narrow therapeutic index and bioavailability problems] and, additionally, there are two brands of warfarin on the Australian market which are not considered interchangeable with each other – as no formal bioequivalence comparison of them has been made [2].

However, where branded warfarin was compared to bioequivalent generic formulations, similar outcomes for patients were observed, indicating that brand name warfarin was not superior to a generic alternative in a clinical setting [13].

Such bioequivalence limits may suggest that a variance of 25% between an originator brand and a generic product is possible. However, this may not actually be the case. A study was performed which investigated 12 years of bioequivalence data submitted to the FDA, comparing the generic and originator measures from 2070 single-dose clinical bioequivalence studies of orally administered generic medicine products approved by the Food and Drug Administration (FDA) from 1996 to 2007. This study showed that the average difference in AUC (area under the concentration time curve) between the generic and the originator was 3.6% and is comparable to differences between two different batches of an originator drug [14]. However, it should be noted that variations between batches of originator drugs may themselves threaten patient safety. In 2012, Patel et al
reported that (in 2010) patients prescribed Lamotrigine (LTG, an anti-epileptic medication) experienced unexplained toxicity [15]. When investigated, the manufacturer (GlaxoSmithKline) accepted responsibility for an altered formulation due to changes made to the manufacturing process.

Generic Medicines in the European Union

The legal situation regarding authorisation of pharmaceutical products in the EU is more complex than in the US, with each member state having a competent authority in addition to the European Medicines Agency [EMA], which oversees EU-wide authorisation of medicines.

The EMA defines a generic medicine as: *a medicine that is developed to be the same as a medicine that has already been authorised (the ‘reference medicine’). A generic medicine contains the same active substance(s) as the reference medicine, and it is used at the same dose(s) to treat the same disease(s) as the reference medicine. However, the name of the medicine, its appearance (such as colour or shape) and its packaging can be different from those of the reference medicine* [16].

Authorisation of a medicine in the EU can be done via three different routes: the Centralised Procedure [CP], the Decentralised Procedure [DCP] or the Mutual Recognition Procedure [MRP] [17]. Additionally, National Procedures [NP] are in place in individual member states, which allow a medicine to be authorised by the competent authority in that specific member state.

The CP, which came into operation in 1995, allows applicants to obtain a marketing authorisation that is valid throughout the EU. It is compulsory for
medicinal products manufactured using biotechnological processes, for orphan medicinal products and for human medicine products containing a new active substance which was not authorised in the Community before 20 May 2004 (date of entry into force of Regulation (EC) No 726/2004) and which are intended for the treatment of AIDS, cancer, neurodegenerative disorder or diabetes. The centralised procedure is also mandatory for veterinary medicinal products intended primarily for use as performance enhancers in order to promote growth of treated animals or to increase yields from treated animals [18]. CP applications are made to the EMA. The EMA performs a scientific evaluation of marketing authorization (MA) applications, and if the evaluation recommends approval of the medicine, the EMA provides their opinion to the European Commission who grant the MA; which is then valid in all EU member states as well as the European Economic Area (EEA).

To be eligible for the MRP, a medicinal product must have already received a marketing authorisation in one Member State. Since 1 January 1998, the MRP is compulsory for all medicinal products to be marketed in a Member State other than that in which they were first authorised. Any national marketing authorisation granted by an EU Member State’s national authority can be used to support an application for its mutual recognition by other Member States [19]. The MRP is based on the principle of mutual recognition, by EU Member States, of their respective national marketing authorisations. An application for mutual recognition may be addressed to one or more Member States. The applications submitted must be identical and all Member States must be notified of them. As soon as one Member State decides to evaluate the medicinal product (at which point it becomes the "Reference Member State"), it notifies this decision to other
Member States (which then become the "Concerned Member States") to whom applications have also been submitted. Concerned Member States will then suspend their own evaluations, and await the Reference Member State's decision on the product. This evaluation procedure - undertaken by the Reference Member State - may take up to 210 days and, if successful, results in the granting of a marketing authorisation in that Member State. When the assessment is completed, copies of the report are sent to all Member States. The Concerned Member States then have 90 days to recognise the decision of the Reference Member State. National marketing authorisations are granted within 30 days after acknowledgement of the agreement [19].

The DCP is similar to the MRP but the difference lies in that it applies to medicinal products that have not received a marketing authorisation at the time of application. With the DCP, an identical application for marketing authorisation is submitted simultaneously to the competent authorities of the Reference Member State and of the Concerned Member States. At the end of the procedure, the product dossier, as proposed by the Reference Member State, is approved. The subsequent steps are identical to the mutual recognition procedure [20].

As in the US, applicants for a marketing authorisation [MA] for a generic medicine in the EU may submit an abbreviated application. According to Article 10(1) of Directive 2001/83/EC [21], an applicant for an authorisation to market a generic medicine is not required to provide the results of pre-clinical and clinical trials if it can be demonstrated that the medicinal product is:

A generic medicinal product or a similar biological medicinal product of a reference medicinal product, which has been authorised under Article 6 of
Directive 2001/83/EC for not less than 8 years. This type of application refers to information that is contained in the dossier of the authorisation of the reference product. This information is generally not completely available in the public domain. Authorisations for generic or similar biological medicinal products are therefore linked to the ‘original’ authorisation. This does not however mean that withdrawal of the authorisation for the reference product leads to the withdrawal of the authorisation for the generic product (case C-223/01, AstraZeneca, judgment of the European Court of Justice of 16 October 2003).

The generic or similar biological medicinal product, once authorised, can however only be placed on the market 10 or 11 years after the authorisation of the reference medicinal product, depending on the exclusivity period applicable for the reference medicinal product [22].

Generic medicine applications typically include chemical-pharmaceutical data and the results of bioequivalence studies, which demonstrate the similarity of the generic product relative to the reference medicine. As stated previously, the tolerance levels involved have been favourably compared to those acceptable for inter-batch variation during production of the originator medicine [14]. The authorising regulatory agency(ies) is referred to the data that were established in the originator product’s application for authorisation for information concerning the safety and efficacy of the active molecule. This is only possible once the data exclusivity period has expired on the originator product’s dossier [21, 23]. The majority of authorisations for generic medicines are granted through the MRP and the DCP. Since the introduction of the DCP, the MRP has mainly been used for
extending the existing marketing authorisation to other countries in what is known as the “repeat use” procedure [23].

EU bioequivalence parameters are similar to those mandated in the US, requiring (for orally administered drugs) that the test and reference products be contained within an acceptance interval of 80.00 – 125.00% of the AUC [area under the concentration time curve], which reflects the extent of exposure at a 90% confidence interval. Also measured is the $C_{\text{max}}$ (the maximum plasma concentration), and $t_{\text{max}}$ (time to maximum plasma concentration). European guidelines, however, also provide a tightened acceptance interval of 90.00-111.11% for narrow therapeutic index drugs [NTIDs] as well as different assessment requirements for highly variable drug products [HVDPs] [24].

As both the terms ‘drug absorption’ and ‘drug bioavailability’ are used in the context of defining bioequivalence it is important to understand the difference between these terms. Drug bioavailability is a subcategory of absorption and is that part of an administered dose of a drug that reaches the bloodstream to become available in the blood plasma. This quantity depends on how and where the drug is absorbed via its route of administration, for example, orally administered drugs will be absorbed through various sections of the gut (often pH dependent) therefore not all of the quantity of the drug ingested may be absorbed to become bioavailable in blood plasma; in contrast, a medication administered intravenously will have a 100% bioavailability. Both the solubility and permeability of a drug are important factors in determining bioavailability the case of orally administered medicines. One criticism of BE studies is that bioavailability is often measured in healthy subjects, not in the patient population.
for whom the drug is intended, and thus may not be an accurate indicator of how bioavailable the drug might be in the target population.

Overall, both EU and US legislation for the authorisation of generic medicines allow for abbreviated applications to be made in the case of generic medicines. In both jurisdictions, pre-clinical and clinical studies do not have to be performed by the generic medicine applicant, but bioequivalence to the originator or “reference” medicine must be demonstrated. This abbreviated application process is often quoted as one of the main reasons for the price difference between generic and originator drugs. However, there is variation in generic medicine prices (e.g., within the single market European Union) unrelated to Research and Development expenditure and greatly influenced by local regulations and reimbursement arrangements that may, in some cases, be disassociated from the costs of manufacture and distribution [9]. Other important influencers include demand-side pressures (i.e., education, engineering, economics, and enforcement), International Non-proprietary Name (INN) prescribing, and, specifically, reference pricing which have been widely adopted by European governments [25-29]. It is also worth noting that generic medicine pricing is being driven further downwards as a result of keen competition in this sector. There is evidence of European generic medicine manufacturers facing competition from Indian producers, and a now-established practice of discounting prices to Governments [9, 30]. Indeed, experts are now recommending that “European countries must continue learning from each other to fund increased volumes” and so exploit such discounts for bulk purchases [29]. As a result of these and other factors, generic medicines are generally between 20 to 90% cheaper than their originator equivalents [31] which has obvious implications for healthcare costs. For example,
in October 2010 in the UK, generic simvastatin (a cholesterol-lowering medicine) cost £1.12 for a pack of 28 (20mg) compared with approximately £30 for a pack of 28 (20mg) of the originator product [32].

A Brief History of Pharmaceutical Regulations

Major Pharmaceutical Legislation in the United States of America

Notable regulations published relating to pharmaceutical regulation in the 20th century began in 1906 with the Pure Drug and Cosmetic Act [PDCA] in the United States. In 1905, a book called The Jungle was published, in which Upton Sinclair wrote about the Chicago meat packing industry. The book described the unsanitary conditions in which animals were slaughtered and processed, including the practice of selling rotten or diseased meat to the public [33]. This book had a major impact on the American people and led the US Congress to pass the PDCA. With this new law, it became illegal to sell contaminated [adulterated] food or meat, and for the first time labelling of food and drugs had to be truthful – meaning that false or exaggerated claims could no longer be made on labels. The Act also required selected dangerous ingredients to be labelled on all drugs and inaccurate or false labelling was called “misbranding” and also became illegal.

The US Congress passed the Federal Food, Drug and Cosmetic Act [FDCA] in 1938 to complement the PDCA. This was largely in response to a public health disaster with a medicine called Elixir Sulfanilamide in 1937. Elixir Sulfanilamide was a sulfa drug sold as an anti-infective. Over 100 people died, most of them children, following ingestion of this medicine due to the fact that it contained diethylene glycol [DEG] as a solvent. DEG is a chemical analogue of antifreeze and is toxic to humans. The company that manufactured the medicine did not perform any toxicity testing prior to marketing the drug as, at the time, there
were no regulations requiring the pre-marketing safety testing of new medicines. The FDCA required, *inter alia*, that new drugs be demonstrated as safe to humans before marketing [34].

The Public Health Service [PHS] Act, which was passed in 1944, was the legal basis for the licensing and gaining of marketing approval of biologic products [35]. Biological products are medicinal products that include vaccines, blood and blood components, allergenics, somatic cells, gene therapy, tissues, and recombinant therapeutic proteins. Biologics can be composed of sugars, proteins, or nucleic acids or complex combinations of these substances, or may be living entities such as cells and tissues. Biologics are isolated from a variety of natural sources - human, animal, or microorganism - and may be produced by biotechnology methods and other cutting-edge technologies. Gene-based and cellular biologics, for example, are often at the forefront of biomedical research, and may be used to treat a variety of medical conditions for which no other treatments are available [36].

The 1962 Kefauver-Harris Drug Amendments [KHDA] added further protection to public health. The KHDA added the requirement that drugs be proven effective for their intended use. With both the 1938 and 1962 laws in place, US regulators were now ensuring that drugs made available to the American public were relatively safe to consume, in addition to being proven effective in treating the disease or condition that they were being marketed in relation to.

In response to the emerging AIDS crisis in the 1980’s, the Orphan Drug Act [ODA] was enacted in 1983 to encourage the development of medicines for conditions that affected small populations by providing monetary and marketing incentives to drug manufacturers. The following year, in 1984, the US Congress also enacted
the Hatch-Waxman Act [HWA], which provided for the marketing of generic medicines, the aim of which was to save Americans money on their medicine bills.

The Biologics Price Competition and Innovation Act of 2009 (BPCI Act) was signed into law, by President Barack Obama, on March 23, 2010. The BPCI Act was an amendment to the Public Health Service Act to create an abbreviated approval pathway for biological products that are demonstrated to be highly similar (biosimilar) to a Food and Drug Administration (FDA) approved biological product. This Act is similar, conceptually, to the Hatch-Waxman Act and it aligns with the FDA's longstanding policy of permitting appropriate reliance on what is already known about a drug, thereby saving time and resources and avoiding unnecessary duplication of human or animal testing [37].

Other pieces of legislation have been, and continue to be, enacted to refine aspects of pharmaceutical manufacturing and good manufacturing practices, in addition to ensuring that modern scientific practices and developments are incorporated into law. Refer to Figure 2, History of Pharmaceutical Regulations – Timeline of Significant Legislations in the 20th and 21st Centuries, for a schematic timeline of the introduction of the major pieces of pharmaceutical regulatory legislation in the US and EU.
Major Pharmaceutical Legislation in the European Union

The first European pharmaceutical directive, 65/65/EEC, was brought into force on 26 January 1965 [38]. It aimed to establish and maintain a high level of protection for public health and required prior approval for marketing of originator medicinal products. Much of the impetus behind Directive 65/65/EEC stemmed from determination to prevent a recurrence of the thalidomide disaster in the early 1960s, when thousands of babies were born with limb deformities as a result of their mothers taking thalidomide as a sedative during pregnancy. This experience, which shook public health authorities and the general public made it clear that, to safeguard public health, no medicinal product must ever again be marketed without prior authorization [39].


The Council adopted directives in 1992 on the wholesale distribution, classification for supply, labelling and packaging, and advertising of medicinal products for human use. The EU also introduced pharmacovigilance (the surveillance of the safety of a medicinal product during its life on the market), requiring Member States to establish national systems to collect and evaluate information on adverse reactions to medicinal products and to take appropriate action where necessary.
A new European system for authorising medicinal products came into effect in January 1995 (via Regulation EEC/2309/93 [42] & Directive 93/41/EEC [43]) along with the establishment of the new European Medicines Evaluation Agency. It offered two routes for authorising medicinal products: a "centralised" procedure, through the European Medicines Evaluation Agency (EMEA) (now the European Medicines Agency (EMA) [44]); and a "mutual recognition" procedure through which applications are made to the Member States selected by the applicant, and the procedure operates by mutual recognition of the national marketing authorisation. Additionally, updates to the requirements relating to the placing on the market of high-technology medicinal products, particularly those derived from biotechnology, were put in place.

The newest piece of major legislation in Europe is the Falsified Medicines Directive [2011/62/EU] [45], effective on 02 January 2013, which aims to protect European consumers against the threat of falsified medicines that might contain ingredients, including active ingredients, not indicated on the labelling, are of poor quality or are in the incorrect dose – either too high or too low. As they have not been properly evaluated to check their quality, safety and efficacy they are potentially detrimental to public health and safety. The term 'falsified' is used to distinguish from the infringement of intellectual property rights, so-called 'counterfeits'. As falsifications become more sophisticated, the risk that these products reach patients in the EU increases every year [46].

**Biosimilars**

The newest incarnation of off-patent medicines are “biosimilar” medicines, also known as “follow-on biologics”. Biosimilar medicines have been a reality in the
European Union for several years and the necessary legal framework was adopted in the EU on 31 March 2004 with the first biosimilar medicines approved by the European Commission in April 2006 [47].

A biological medicine is a medicine whose active substance is made by or derived from a living organism. For example, insulin can be produced by a living organism (such as a bacterium or yeast) which has been genetically manipulated to produce insulin [48]. A “biosimilar” medicine is one that is similar to a medicine of biological origin that has already been authorised (known as the biological reference medicine). Biological products are fundamentally different from standard chemical products in terms of their complexity, and it is unlikely that the biosimilar product will have an identical structure to that of the reference product, thereby requiring evidence of safety and efficacy before approval. In this regard, biosimilars are different from the (to date) more familiar generic products.

As with other generic medicines, a biosimilar medicine undergoes testing to ensure that it is as safe and effective as the reference product. However, due to the complex method of production, the active substance may differ slightly between the two medicines and so, additional safety and efficacy studies may be required on a case-by-case basis.

Since biosimilar and biological reference (originator) medicines are similar but not identical, the current recommendation is that the patient should be prescribed the same formulation (either the originator or biosimilar formulation) on each occasion [48]. See Figure 3 Examples of Biosimilar Products (Adapted from [49]) for some examples of originator (i.e. reference) biologics and their biosimilars.
Drug Development

Development of new drugs is a complex and costly process. It generally takes 10-15 years, and studies have shown that it can cost between US$800 million to US$2 billion to get a new drug to market, with similar, or even higher, costs for development of biopharmaceuticals [biologics] [50].

Research and Development [R&D] involves discovery [preclinical studies] and development [clinical studies] of New Chemical Entities [NCEs] also known as New Molecular Entities [NMEs]. It is worth noting that of about 10,000 NCEs investigated to potentially treat a disease, only 250 might make it to animal testing and, of these, approximately 5-10 will qualify for testing in humans. Between 19 and 30% of Investigational New Drugs [INDs] that begin Phase 1 trials make it to marketing [51], meaning that only 1-2 of the original 10,000 NCEs will result in a marketable product.

An experimental medicine, also known as an Investigational Medicinal Product [IMP], is first tested in *in vitro* laboratory studies and *in vivo* animal studies. Following success here, the testing can move to the clinical phase where the IMP will be used for the first time in human clinical trial volunteers. Refer to Figure 4, *Schematic of Drug Development Process* (adapted from [52]), for an illustration of the process.

Naming of New Drugs

During the R&D process, a new pharmaceutical substance is given an International Non-proprietary Name [INN] or generic name, in addition to the name that may eventually become its proprietary, or brand, name. Each INN is unique, globally recognised and is public property.
Non-proprietary names are intended for use in pharmacopoeias, labelling, product information, advertising and other promotional material, drug regulation and scientific literature, and as a basis for product names, e.g. for generics. Their use is normally required by national or, as in the case of the EU, by international legislation. As a result of ongoing collaboration, national names such as British Approved Names (BAN), Dénominations Communes Françaises (DCF), Japanese Adopted Names (JAN) and United States Accepted Names (USAN) are nowadays, with rare exceptions, identical to the INN. Names which are given the status of an INN are selected by the World Health Organisation on the advice of experts from the WHO Expert Advisory Panel on the International Pharmacopoeia and Pharmaceutical Preparations.

An important feature of the INN naming system is the use of a common “stem” which indicates the activity of the substance and the pharmacological group to which it belongs. The stem is generally placed at the end of the name, but in some cases it may be placed at the beginning or in the middle of the name. For example: substances having \textit{–adol/-adol} as the stem indicates an analgesic (e.g. tramadol); \textit{–mab} indicates a monoclonal antibody (e.g. infliximab); \textit{-azepam} indicates a diazepam derivative (e.g. temazepam) and \textit{–vir} indicates antiviral agents (e.g. acyclovir). All of the stems recommended by the WHO are contained in the “stem book” along with guidance for their use [53]. The INN, containing the common stem, provides a single, unique name which enables healthcare professionals to recognise the substance and the family of similar pharmacological substances to which it belongs. The INN is generally the name under which the generic form of a drug is marketed.
Pre-Clinical Research

The earliest stage of development of a new drug begins with the synthesis and purification of the new chemical moiety, or the screening of existing compounds for potential use as drugs. The aim of pre-clinical research is to determine whether the drug is reasonably safe for potential use in humans, and sufficiently effective against a disease target in chemical tests or animal models. During pre-clinical studies, the pharmacology of the new drug in addition to its pharmacokinetics: absorption, distribution, metabolism, excretion & half-life; and pharmacodynamics: mechanism of action and estimates of therapeutic effects, are assessed. Initial studies relating to toxicology including carcinogenicity, mutagenicity, and teratogenicity are also carried out, as are efficacy studies on animals.

Clinical Trials

Once permission has been received from the appropriate regulator to administer a new drug to humans, clinical studies may commence. Clinical studies required to bring a new drug to market generally take place over three phases as follows:

- **Phase 1:** Safety studies on healthy volunteers. Typically involve 20-80 healthy volunteers (women of childbearing potential are excluded). The emphasis is on drug safety and on the building of a safety profile for the drug in humans.

- **Phase 2:** Clinical studies on a limited scale to determine efficacy of the drug. Typically involve 100-300 individuals who have the target illness. Patients receiving the drug are compared to similar patients receiving a placebo or another drug, and safety evaluations continue.
- Phase 3: Comparative studies on a large number of patients. Typically involve 1000-3000 patients. The emphasis is on safety and effectiveness and studies investigate different populations and different dosages as well as evaluating the new drug in combination with other drugs. Data gathered in a phase 3 trial are used to determine the risk versus benefit profile of the drug.

Following successful completion of clinical trials, the entirety of the information about the drug is compiled into an application and submitted to the relevant competent authority [e.g. FDA in the US, or EMA in Europe]. The competent authority reviews this application, and additional information may be sought from, or discussions held with, the applicant before the regulator makes its decision. The regulator will, after assessing the scientific data pertaining to the new drug, either allow it to be marketed, or deny approval to the applicant.

**Registration**

The next step in bringing a new medicine to market is the filing of an application with the health regulatory authority of a country in order to obtain approval to market the new medicine. This step is known as registration. In the US, a New Drug Application (NDA) or Biologic Licence Application (BLA) is filed with the US Food and Drug Administration (FDA). In Europe, a Marketing Authorization Application (MAA) is filed with the European Medicines Agency (EMA), or local competent authority, dependent on the approval route being used. A description of the medicine's manufacturing process along with quality data and trial results are provided to the health regulatory authorities in order to demonstrate the safety
and effectiveness of the new medicine. If approval is granted, the new medicine can be marketed for use by patients.

**Post-Marketing Surveillance**

Post-market surveillance studies [also called Phase 4 trials] of the drug continually assess the safety of the drug in the marketplace. This may include reporting and investigation of the incidence and severity of rare adverse reactions, cost-effectiveness analyses, comparative trials, and quality of life studies.
Where Do Generic Medicines Fit Into This Process?

Applications for marketing approval of generic medicines [i.e. the submission of an ANDA in the US, or a generic MAA in Europe] are made at approximately the same time point as the registration step for originator (i.e. proprietary) medicines. Generic medicine applications do not need to contain the pre-clinical and clinical studies required for originator medicines, with relatively simple bioequivalence studies being acceptable in their place, as discussed earlier [8, 16].

Referring to Figure 4, it can be seen that the difference in the cost of generic medicines is primarily due to the fact that investment in generics is significantly less than for new originator medicines. Without the need to recoup the costs of pre-clinical and clinical studies, generic manufacturers can price their product lower than the originator product. However, as referred to previously, the market price of the product can be considerably influenced by end-user and prescriber perception, local regulations and reimbursement models [9].

From a production point of view, however, the cost of manufacturing an originator or a generic will probably not differ significantly as they are both manufactured under the same industry standards and conditions. In fact, it is not uncommon for the manufacturer of an originator product to become a manufacturer of a generic version of the drug, once the patent for the drug has expired and it becomes open to generic competition [2]. From an economic perspective, this allows the company to continue recouping the cost of their capital and R&D investment from first introducing the product to the market.
Are Generic Medicines Really The Same As The Originator Medicines?

It has been clearly shown that, at least at a physiological level, generic medicines behave very similarly to their originator counterparts. As described earlier, an assessment of 12 years of bioequivalence data submitted to the FDA, comparing 2070 single-dose clinical bioequivalence studies of orally administered generic medicine products approved by the Food and Drug Administration (FDA) from 1996 to 2007, demonstrated that the products did not differ significantly [14]. Similarly, referring to clinical efficacy, Kesselheim et al (2008) published an extensive systematic review and meta-analysis (referred to previously) that were favourable towards use of generic drugs in treating cardiovascular disease [13]. In another study they reported that, for anticonvulsant drugs, “evidence does not suggest an association between loss of seizure control and generic substitution” [54]. Further, many studies have demonstrated that initiation of treatment with generic medicines or switching to generic medicines are not associated with poorer patient outcomes. Specifically, Amit et al in 2004 showed that a generic formulation of propafenone, used to treat atrial fibrillation, was found to be at least as safe as the originator drug [55]. Additional evidence of safety in use of generic antipsychotic medicines was provided by Araszkiewicz et al [56] while the safety and efficacy associated with switching of drugs has also been positively reported [57, 58].

Researchers have, however, also reported patient concerns related to generic medicines. These studies range from qualitative assessment of perceptions in specific patient cohorts [59] to general lay/consumer knowledge [60, 61], versus knowledge of professionals [62, 63]. Many of these studies focus on the influence of relative cheapness on perceptions and use of generic medicines [64, 65]. Some publications have shown that consumers felt that a generic medicine did not work either as effectively, or at all, in
comparison to when they were taking the originator medicine [66]. For example, reports from patients show that symptoms of depression, which returned while taking a generic medicine, abated again when they switched back to the originator medication [66]. Researchers investigating the efficacy of generic bisphosphonates in the management of osteoporosis demonstrated that they resulted in poorer increases in bone mineral density than branded products [67] and postulated that reasons for this may include higher levels of gastrointestinal adverse events and poor tolerance of generic formulations associated with an increased likelihood of generic particulate matter adhering to oesophageal mucosa [68]. However, newly recommended criteria for the evaluation of treatment failure in osteoporosis may stimulate further research into this clinical challenge [69].

In treatment of epilepsy, significant problems have been reported, including breakthrough seizures and increased side effects following a switch to a generic antiepileptic drug [AED] [70]. Additionally, Jain (1993) ascertained that 26 of 131 cases of carbamazepine failure reported to the drug maker were associated with seizure increases following a switch to a generic formulation. Seizure control returned to baseline when the brand formulation was re instituted [71]. Mayer et al (1999) compared patients who were receiving a generic extended-release carbamazepine formulation with patients taking a branded formulation, in an unblinded trial, and found that 9 of 13 subjects experienced adverse effects when on the generic formulation, with AUC fluctuations that are acceptable within current FDA guidelines [72]. It can be concluded, therefore, that at least in the case of AEDs, bioequivalence, as defined in regulations, does not always correspond to therapeutic equivalence because of the permitted range, evaluation methods and individual variation [73], although this has been refuted in an
extensive meta-analysis by Keselheim et al [54] who found that generic substitution had no impact on efficacy of seizure control.

Incidents such as those described above have resulted in caution being expressed by professionals regarding the safety and effectiveness of generic medicines, albeit in a minority of situations [74, 75]. This is contrary to the fact that there is strong evidence that consumers believe that generics are less expensive (and therefore better value) than brand-name drugs, and are as safe [76]. Indeed, the debate is further fuelled by incisive systematic reviews of the published literature. For example, Talati et al (2012) assessed the efficacy, tolerability, and safety of innovator versus generic antiepileptic drugs, and demonstrated that (albeit with a low strength of evidence) initiating treatment with an innovator or generic antiepileptic drug will provide similar efficacy, tolerability, and safety but that switching from one form of medication to the other may be associated with more hospitalizations and longer hospital stays [77]. Some experts have stated that switching between originator and generic drugs may actually be unethical, raise the cost of treatment, with additional clinic visits and laboratory tests [78, 79]. Similar arguments are made when addressing the concept of therapeutic substitution, whereby there may be an attractive price differential between established drugs whose patents have expired and for which generics are available and newer (or branded) medicines within the same therapeutic class, as researchers have made the point that direct evidence to support equivalence may be lacking [80-82].

While the active pharmaceutical ingredient (API) does not differ between originator and generic medicines, other (inactive) ingredients, known as excipients, may be different and a number of pharmaceutical excipients are known to have side effects or contraindications [83]. As excipients may differ between originator medicines and
generic preparations which have been shown to be bioequivalent and therefore substitutable, there needs to be an awareness in the medical/healthcare community that where a generic preparation contains an excipient which is not part of the originator preparation, there is the potential for the generic formulation to cause problems in a patient who had no issues in tolerating the original preparation.

Evidence has been published that differences in excipients between originator medications and their generic counterparts can cause problems. For example, allergic reaction has been reported to croscarmellose sodium used as excipient in a generic furosemide preparation in a patient who had previously been taking branded furosemide without incident [84]. (Croscarmellose is used in injectable preparations as a suspending agent to promote solubilisation of compounds with poor water solubility; it is also present in tablets as binder, glidant and antiadherent).

Similarly, a lactose-intolerant patient with an arrhythmia who is switched from one formulation of antiarrhythmic drug to another that contains a lactose-based excipient may experience gastrointestinal disturbances which could affect gut transport time and overall drug absorption, thereby affecting systemic levels of the drug [85]. Studies have also reported significantly different serum levels of antiarrhythmic drugs associated with originator products and their generic equivalents, in addition to observing patients’ symptoms recur following a switch to a generic formulation. These observations have led to the conclusion that there is evidence that formulation substitution in the cardiovascular arena has risks [85].

More broadly, allergies to excipients contained in topical steroids have also been well documented [86] - with these allergens being contained in both originator and generic
preparations. Saccharose, an excipient with potential side effects, was seen in generic preparations of phenobarbitol used to treat epilepsy in Mauritania [87]. Lactose and saccharose are contraindicated in people with lactase or saccharase deficiencies and as the frequency of these enzyme disorders is high in African populations [88], this suggests the potential for negative clinical reaction to such medicines in African patients.

Therefore, while bioequivalence between an originator medicine and a generic equivalent may have been proven, as required by the current regulatory guidelines, given the differences in other ingredients it is incumbent on prescribing physicians to remain vigilant to the potential risks, and exercise caution in the substitution of a medication with an equivalent. This is applicable to both substitution of a branded medication with a generic equivalent and to switching between different, equivalent, preparations of generic medications (e.g. the same generic medication produced by different manufacturers).

This, however, is not an effect limited to use of generic medicines. As described earlier, Patel et al reported that (in 2010) patients prescribed an anti-epileptic medication experienced unexplained toxicity [15] which, when investigated, was found to be due to altered formulation.

Despite this, regulators have, in some cases, adopted a cautious approach in legislating for potential risks associated with generic substitution, in particular possible challenges relating to continued efficacy and safety of treatment under defined circumstances. In July 2011, the Danish Government banned generic substitution for immunosuppressants (specifically, cyclosporine and tacrolimus) due to issues relating to the possible need for increased testing requirements following use of generics in
transplant patients [89]. Similarly, the British National Formulary (BNF) currently recommends brand prescribing for a number of medicines and drug classes, namely modified release diltiazem [90 p132]) and cyclosporine [90 p583], while in July 2008 the Northern Ireland Health and Social Care Board issued an extensive list of medicines considered unsuitable for generic prescribing [91] which included narrow therapeutic index drugs, modified release preparations, controlled drugs including patches, inhalers, and multi-ingredient products.
Usage of Generic Medicines in Ireland, a Case Study

Irish healthcare spending in 2010 accounted for 9.2% of GDP [92], with total expenditure on pharmaceuticals amounting to €2.2 billion, and public expenditure on pharmaceuticals (administered by the Primary Care Reimbursement Service, PCRS) amounting to €1.9 billion. Public expenditure on pharmaceuticals was one of the fastest growing components of public health expenditure over the period 2000 to 2010. It increased by 158.5 per cent in real terms and accounted for 12.9 per cent of total public health expenditure in 2010 (up from 10.1 per cent in 2000) [92].

State assistance towards the cost of pharmaceuticals is available under a number of different schemes. The General Medical Services (GMS, or medical card) Scheme provides free public health care (including GP care and prescription pharmaceuticals) to those who satisfy an income means test. In April 2011, over 1.6 million individuals had a medical card, accounting for 36.2 per cent of the population. A further 2.6 per cent of the population were eligible for free GP services (but not prescription pharmaceuticals) under the GMS Scheme (known as GP Visit card holders) [93]. Non-medical cardholders avail of State assistance towards the cost of prescribed pharmaceuticals under a number of Community Drugs Schemes (CDS). The three largest (in expenditure terms) are the Drugs Payment (DP), Long Term Illness (LTI) and High Tech Drug (HTD) schemes. At the time of writing, all those ineligible for a medical card were eligible for the DP Scheme, whereby the State pays the full cost of prescription pharmaceuticals and certain appliances above a monthly threshold of €132 per family.

Penetration of generic medicines into the Irish market is amongst the lowest in Europe. See Figure 5: Market Shares (By Volume) of Generic Medicines in Europe in 2006
(data from [94]). Furthermore, in a report written by the NCPE for the Irish Department of Health and Children (DOHC) in 2008 it was reported that generic prescribing in Ireland had fallen from over 22% by volume in 1997, to just over 19% in 2007 [93]. As a result of this poor penetration by generic medicines, Irish expenditure per 1000 inhabitants per annum is ten times that of Sweden, putting in perspective the considerable need to quickly realize the substantial savings that are possible without compromising patient safety or efficacy of treatment.

In 2008, approximately a quarter of all prescriptions dispensed on the GMS, DP and LTI schemes had an available generic equivalent [95]. That translated into €227.76 million which was spent on originator medicines where there was an equivalent, less expensive, generic product available representing a potential area for cost saving to the Irish state. Moreover, from the NCPE’s 2008 figures, an immediate opportunity for increase in use of generics in Ireland can easily be seen, as the DP/LTI figures show a difference of 7% in the proportion of prescriptions that were for generics compared to generic prescriptions from the GMS [96].
Cost-Saving Potential in Ireland

The net cost of the Irish Community Drug Schemes more than doubled in a seven year period, from €1.024 billion in 2001 to more than €2.289 billion in 2007 [96]. The increase is partly explained by a “low” price fixed in 1992, subsequently renegotiated, and 50% mark-up (on ingredient costs) and dispensing fees agreed with dispensing pharmacists in parallel with an ageing population accessing the GMS scheme. The four schemes together account for 98% of prescriptions and 99% of expenditure in the community setting [97].

Cost-saving opportunities, including something as straightforward as closing that 7% difference between GMS and DP/LTI generic prescription figures, may be critical to the Irish state, in an era when healthcare costs are escalating. Furthermore, it was reported in 2003 that there was the potential for 40% of medicines prescribed on the GMS to be dispensed generically [98]. As increasing numbers of originator medicines reach the end of their patent/exclusivity periods, thereby allowing generic competitors to enter the market, this area represents an increasing potential for cost savings for the public purse.

Total expenditure on originator medicines in Ireland rose from €120 million in 2004 to more than €220 million in 2008 [99]. In 1997, the average cost per dispensed item under the GMS scheme was €11.20 as compared with €23.27 in 2007. Factors contributing to the increase in drug expenditure include the “product mix” (the prescribing of newer, more expensive medications) and the “volume effect” (comprising of the growth in the number of prescription items issued). In 1997, twenty million prescription items were issued under the GMS scheme. This increased over two-fold to 44.35 million items in 2007. The year on year increase in pharmaceutical expenditure in Ireland is amongst
the highest in Europe with medicines, in 2009, accounting for approximately 13.5% of total healthcare spending [100].

Healthcare costs, as previously demonstrated, may be somewhat mitigated by increased prescription of generic medicines. It has been recommended that the State examine the price it pays for generic medications and encourage greater INN prescribing by doctors [95]. In recent years, a trend towards the prescription of generic medicines has been seen worldwide. For example: in the US, in 1984, only 14% of prescriptions were for generic medicines. This had increased to 66% in 2006 [95] and by 2011, 78% of prescriptions written in the US were for a generic medicine [8]. In the UK, generic medicines accounted for approximately 83% of all prescriptions written in 2009 and 2010 [101]. [That rate, incidentally, is generally considered to be in the region of the maximum expected rate of generic prescribing]. A key driver for such a high rate of generic prescribing has been the training of UK physicians to prescribe by INN where possible, something which is subsequently continued and encouraged in practice [102] and is one of multiple initiatives used in Scotland with particular emphasis on PPIs and statins [103]. It is worth noting that in Ireland, in 2007, generic prescribing comprised 2.6% unbranded generics versus 16.4% branded generics (78) and is, thus, a target for education regarding generic usage. Indeed, a related aspect of branded versus unbranded generic prescribing is that there is evidence of confusion where patients are dispensed a different branded generic on each pharmacy visit, resulting in pharmacist (and, presumably, physician) resources being invested in explaining to the patient that their new drug is the same as the previous one [104]. A lesson for Ireland may be that such patient confusion could be avoided if related education of patients is introduced with implementation of the new policy.
An increase in use of generics is associated with significant cost savings, for example in 2010 alone, the use of generics in the American health system saved $158 billion, an average of $3 billion every week [25] and a study by the Generic Pharmaceutical Association (GPhA) showed that prescribing of generics has saved the US economy $931 billion between 2001 and 2010 [105].

In mid 2010, the Irish Minister for Health announced plans to introduce new legislation to allow the introduction of reference pricing and to permit generic substitution/medicine interchangeability in Ireland. A report entitled the Proposed Model for Reference Pricing and Generic Substitution, which describes the model to be implemented in Ireland, indicates the reason for the proposed changes:

Demographic changes over the next decade will have a significant impact on the demand for and the delivery of health care in Ireland. Pharmaceutical expenditure accounts for a large proportion of overall health care expenditure. In 2008, the Health Service Executive paid for approximately 65 million prescription items at a cost of over €1.9 billion. As a result of demographic changes and prescribing trends, the number of prescription items is estimated to increase to 105 million by 2021 at cost of €2.4 billion. The current system is unsustainable. To ensure that patients can continue to access innovative and affordable medicines, new pricing and reimbursement approaches are required, along with changes in prescribing practices. [106]

At the time of writing, the current situation in Ireland requires that the pharmacist supply only the medicine indicated by the prescribing physician, even if there is a cheaper, generic version available. The new legislation would require the dispensing pharmacist to notify the patient/customer if a lower-priced, (probably generic)
alternative were available, and to allow that alternative to be dispensed. It seems reasonable to suggest that, given the success of INN prescribing in the UK [107], its adoption by physicians practicing in Ireland would complement the pharmacy-based approach described above.

**Reference Pricing & Generic Substitution**

With reference pricing, a common reimbursement price or reference price, is set for a group of interchangeable medicines based on the price of a “reference drug” which is chosen from that group of drugs [25, 103]. The reference drug will be as safe and effective as the other available drugs in the group and may or may not be a generic medicine. The price of this reference drug is the price paid by the State, and if the patient/consumer wishes to have a different, more expensive, drug to the reference drug, they must pay the difference in price themselves [107]. Provision is generally made for prescribers to prohibit substitution for clinical reasons. In these instances, patients do not face any additional costs if the prescribed product costs more than the reference price.

At the time of writing, neither generic substitution nor reference pricing are permitted in Ireland despite being used in many other countries both in Europe and elsewhere. In these countries, the pharmacist can substitute medicines that have been designated as interchangeable – that is: a medicine of the same quality and clinical efficacy, but of a lower cost, can be dispensed in place of what was prescribed.

However, despite evident success in a number of countries, it has been argued that additional savings may be possible without impacting the continued efficacy or safety of patient treatment. A 2007 study by Kanavos [108] reported that the UK National Health Service was reimbursing for generic medicines at too high a price, and that a considerable proportion of the reimbursed price accrued to the distribution chain in a
fashion that resembles standard retail models. Indeed, it was claimed that this overpayment effectively constituted a subsidy to pharmacists (intended or otherwise). Analogous overpayments were reported in a study of pharmacy discounts in France [109] where control of pharmaceutical expenditure has been a national policy priority for many years and health system measures have included reference pricing, generic substitution and international non-proprietary name (INN) prescribing. However, as in other markets, generic manufacturers and wholesalers offer discounts, rebates or promotions to pharmacies to gain an advantage over competitors, meaning that health insurance in France may be overpaying for generic medicines. As Ireland moves towards a formalized generic medicine policy, an opportunity presents itself to ensure the reimbursement costs are close to market price (including savings associated with volume discounts referred to earlier) and that the benefits of the new policy do not accrue disproportionately to the pharmacists and their wholesalers and medicine distributors.

**Concerns**

While the main objective for the introduction of generic substitution and reference pricing is to reduce costs related to healthcare for both the consumer and the State, the concept of reference pricing is not without its concerns. The Irish Pharmacy Union (IPU) warned that reference pricing could lead to shortages of medicines and the Irish Pharmaceutical Healthcare Association (IPHA) stated that Ireland currently has a fair and equitable single-tier system whereby all patients, regardless of income, have access to secure supply of the medicines which their doctors believe are most suitable for them [110, 111]. The IPU and IPHA believe that should the Health Services Executive [HSE] set the reference price at that offered by the lowest potential supplier, it could give rise to patients being dependent on one supplier, which
could, perhaps, have very limited infrastructure or commitment to the Irish market. This, however, seems at odds with the market situation whereby smaller countries (such as Lithuania which has a population comparable to Ireland) obtain sufficient supplies of products including generic medicines at considerably reduced prices [112] and may, actually, represent an aversion to erosion of profits rather than accurately reflecting the market.

Concerns have also been expressed by organisations such as the Irish Medical Organisation (IMO) and Irish College of General Practitioners (ICGP). During a working group meeting held in January of 2010, the ICGP cautioned that switching of medicines may not be suitable and also that when determining which products are substitutable “the tests of bioequivalence must be robust” [113]. This point regarding equivalence is, as referred to previously, equally relevant to variability between successive batches of originator or generic products.

**Acceptance of INN prescribing and Substitution by Prescribers in Other Countries**

When generic substitution was first introduced in Australia (the Brand Substitution Policy (BSP); introduced in December 1994 [114]), two studies were conducted exploring medical practitioners’ views on generic medicines and generic substitution. The first study, conducted in 1995, five months after the government permitted generic substitution by pharmacists, was a national telephone survey of GPs. Out of a total of 71 GPs, 28 (39%) said ‘no’ to generics substitution, 22 (31%) said ‘yes’ to substitution and 21 (30%) were ambivalent [115]. The most common reason cited by those opposed to generics prescribing and substitution was that it would cause confusion among patients, particularly the elderly, because generic brands were often of different colours and shapes. (This argument ignores the fact that packaging and presentation of originator
medicines may also differ depending on country of origin if sourced via parallel importation). Other reasons given were that it was a doctor’s responsibility, not a pharmacist’s, to decide on medication and that using generics meant less money for research. There were also concerns about bioavailability, adverse reactions to generics and the need for a free enterprise environment [115]. Despite presumably greater familiarity with generic medicines, similar views were expressed by some of the doctors in the second study, which was conducted in 2002 [115].

Analogously, in Sweden, researchers saw that while generic substitution was implemented in 2002, only 60% of the possible indicated savings were made in the first year, due somewhat to the mix of generic and originator products stocked by pharmacists [116]. Subsequent studies by Anderssen et al showed that gender and age influenced Swedish patients' generic medicine use [117] and further documented rational use of generic medicines through the establishment of drug and therapeutic committees, development of guidelines, academic detailing, continuous benchmarking of prescribing patterns and financial incentives that have led to effective implementation of a generic medicine policy by stakeholders recognizing the need to conserve resources [118].

In the US, individual physicians have expressed strong opinions about generic medicines over the years, with opponents of their use generally being more vocal. In 1997, Banahan and Kolassa [119, 120] reported a comprehensive analysis of physicians' attitudes toward generic medications, finding that overall, physicians' attitudes toward generic medicines were fairly neutral, as indicated by their answers to two key questions from their nationwide survey. In a separate study (from 2001), respondents expressed modest support for generic substitution, but had doubts about originator-generic equivalence [121]. More recently, Shrank et al have reported studies addressing
the relationship between generic medicine prescribing and physician practice location and specialty (i.e. higher income catchment areas equated to higher generic prescribing rates and generalist physicians prescribed more generic medicines than specialist physicians) [122]. Shrank et al have also shown that persistence in generic medicine use is higher than with branded products in those patients benefitting from incentives offered by medical insurance companies and pharmacy drug purchase plans [123]. Perhaps most interesting is that, in 2012, Shrank et al found that a meaningful proportion of physicians expressed negative perceptions about generic medications, representing a potential barrier to generic use. The researchers recommended that policymakers trying to encourage generic use should consider educational campaigns targeting older physicians [123].

Similar results were seen in a study carried out amongst Irish prescribers in 1997, which showed that the majority of prescribers were concerned about the reliability and quality of generic medicines [124], and the study concluded that education of stakeholders would be necessary to improve the level of INN prescribing in Ireland. An additional survey in 1997 indicated that over a third of Irish GPs believed that generic medicines were unreliable and of poor quality and 50% of pharmacists believed that some generic medicines were unreliable [125]. The United Kingdom consistently has higher rates of generic prescription than Ireland, and this is generally thought to be due to the fact that Government policy in the UK actively promotes INN prescribing from medical education to subsequent ongoing practice (as described earlier) through processes of monitoring or prescribing of generic versus originator/patented products. The introduction of fundholding practices provided further encouragement from a financial perspective [126], whereby medical practitioners’ fixed budgets provided an explicit incentive to contain costs, which in turn encouraged INN prescribing.
Previous Attempt at Improvement of Use of Generic Medicines in the General Medical Services Scheme in Ireland

In 1993, a drug budgeting arrangement called the Indicative Drug Target Savings Scheme [IDTSS] (also referred to as the Indicative Drug Budgeting Scheme) was introduced in Ireland as a result of a voluntary agreement entered into between the Irish Medical Organisation and the Department of Health [125]. The purpose of this scheme was to curtail spiralling GMS prescription costs by encouraging rational and cost-effective prescribing [126, 127]. With this agreement, an annual “indicative drug budget” was calculated for each participating GMS GP, based on a combination of the doctor’s previous prescribing costs and the national average [127].

Typically, 50% of any savings made on these indicative drug budgets, achieved primarily through use of increased prescribing of generic medicines, were returned to the prescribing physician [128]. All savings had to be invested in the development of the general practitioner’s own practice. There were no penalties for overspending.

A report reviewing the IDTSS in 1997 indicated that the scheme saved IR£13.5 million [i.e. €17.14 million] during 1993-1994 [129]. Additionally, it showed that even those prescribers who exhibited lower-cost and fewer-item prescribing per patient, prior to implementation of the scheme, were successful in reducing their cost per item further through increased use of generic prescriptions [126]. The main conclusions from this report included that there were changes in prescribing behaviours, seen as enhanced prescribing of generic medicines, leading to lower drug costs per patient. Also, there were no discernible negative effects on overall quality of prescribing observed.

A study of the IDTSS by Walley et al showed that the IDTSS encouraged changes in prescribing practice among low and medium cost prescribers, but had no apparent effect in higher cost prescribers. The changes were relatively short-lived with a similar rate of
rise of costs across all groups by the third year of the scheme (1996) [126]. This is broadly similar to the effects of GP fundholding in the UK, where new fundholders dramatically reduced their prescribing costs, but where there were similar rates of rise of prescribing costs after 2-4 years in both fundholding and non-fundholding practices [128].

Despite the reported savings in the first year of the scheme [IR£13.5 million in 1994 [130]], the scheme was not entirely successful; 27% of GPs never achieved any savings in the first 4 years of the scheme [126]. Since December 2005, however, a freeze was placed on this scheme [128]. This may have a factor in the previously mentioned fall in prescribing of generic medicines seen between 1997 and 2008 in Ireland.
Conclusions

While acceptance of the definition of a generic medicine is ostensibly similar worldwide, there are some discrepancies between different jurisdictions, particularly related to determination of bioequivalence. For example, Narrow Therapeutic Index drugs have distinct and different bioequivalence acceptability in the EU that is not in place in the US [127]. Differences such as this, in addition to the fact that components of a generic medicine [with the exception of the API], the appearance of the medicine and its packaging, can differ between apparently equivalent originator and generic medicines have led to publication of reports describing variability in efficacy and adverse events [131]. However, in a balanced debate, these studies and expressions of distrust should be evaluated alongside the many reports that have demonstrated comparable effectiveness and acceptability between generic and originator medicines [66, 67, 74, 124].

Researchers have explored the attitudes and beliefs of stakeholders in the medicines process (that is: prescribers, dispensing pharmacists and patients/end users) demonstrating a spectrum of perceptions and opinion which are influenced by factors such as geography, age and demographics [54-56]. This information clearly demonstrates that if countries are to take advantage of the apparent economic benefits associated with generic medicine use, at least some of their “demand side” [118] activities should focus on education and enforcement to address the excessively sceptical perception of these products. Such approaches to enhance adoption of generic medicines should also be complemented by in-depth analysis of the potential disadvantages of generic products, such as potential variation in quality and formulation [25-29] and associated effects. However, it is probable that existing pharmacovigilence/surveillance systems, which are in place for all human medicines, will be sufficient for monitoring of
these. It cannot, however, be disputed that the reputation and perception of reliability of generics needs improvement in the eyes of those healthcare professionals and patients who have articulated poor opinions of them.

The economic benefits of the use of generic medicines cannot be denied; and in many countries their use is essential to control healthcare spending. Given that the majority of patient-doctor encounters result in the writing of a prescription [132], the cost of the medicine prescribed is of interest both to the patient/consumer and the State. The potential cost savings associated with the use of generic medicines must be considered by the bill-payers. In this paper, we have focused on Ireland’s emerging policy on generic medicine use. With Ireland now poised to make the legislative changes required in order to take advantage of generic substitution and reference pricing, the onus is on Ireland’s Health Service Executive, as well as the prescribers and dispensers of medicines, to ensure that they are fully informed of all the complexities associated with the use of generic medicines.

It is also important to learn from lessons of the past and to take into account previous attempts at increasing prescription rates of generic medicines in Ireland, such as the Indicative Drug Target Savings Scheme [IDTSS], described earlier. Additionally, the Irish government and policy makers may find it useful to look at how generic substitution was successfully implemented in other countries and to take advantage of the depth of information and research available from other jurisdictions which have previously adopted generic substitution and reference pricing. It is in the best interests of the Irish healthcare system for its leaders to learn from the successes and challenges that have already been experienced by other countries such as the UK, France, Germany, Sweden and Lithuania, amongst others. In doing so, education of all
stakeholders, including physicians and allied professionals and, in particular, end-users will be pivotal for the appropriate implementation and acceptance of policies for generic substitution/medicine-interchangeability and reference pricing in Ireland.

With many medicines hitting the so-called “patent cliff”, generic drug usage, already trending upwards, is likely to continue to increase in the coming years, with generic medicines now being, primarily for economic reasons, a reality of modern healthcare systems.
Competing Interests

The authors have no competing interests.
Authors’ Contributions

SD researched and wrote this review. WC, BS and CD provided guidance, critical review and revision of the manuscript. All authors read and approved the final manuscript.
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Endnotes

*For the purposes of this article, the terms “generic drug” and “generic medicine” are considered interchangeable, and therefore, for simplicity of language, only the term “generic medicine” is used throughout.
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Illustrations and Figures

Figure 1: Originator (NDA) versus Generic (ANDA) Review Process Requirements

Figure 2: History of Pharmaceutical Regulations – Timeline of Significant Legislations in the 20\textsuperscript{th} and 21\textsuperscript{st} Centuries

Figure 3: Examples of Biosimilar Products

Figure 4: Schematic of Drug Development Process

Figure 5: Market Shares (By Volume) of Generic Medicines in Europe in 2006 (reproduced with permission from the European Generic Medicines Association)
Figure 1: Originator (NDA) versus Generic (ANDA) Review Process

Requirements

<table>
<thead>
<tr>
<th>NDA Requirements</th>
<th>ANDA Requirements</th>
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<tbody>
<tr>
<td>1. Labelling</td>
<td>1. Labelling</td>
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<td>2. Pharmacology/Toxicology</td>
<td>2. Pharmacology/Toxicology</td>
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<td>3. Chemistry</td>
<td>3. Chemistry</td>
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<td>5. Controls</td>
<td>5. Controls</td>
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<td>7. Inspection</td>
<td>7. Inspection</td>
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<td>8. Testing</td>
<td>8. Testing</td>
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<td>9. Animal Studies</td>
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<td>11. Bioavailability</td>
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</tbody>
</table>
Figure 2: History of Pharmaceutical Regulations – Timeline of Significant Legislations in the 20th and 21st Centuries
Table 3: Examples of Biosimilar Products

<table>
<thead>
<tr>
<th>Reference biologic (active substance)</th>
<th>Manufacturer</th>
<th>Biosimilar products</th>
<th>Manufacturer</th>
<th>Activity</th>
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<tbody>
<tr>
<td>Genotropin (somatropin)</td>
<td>Pfizer</td>
<td>Valtropin</td>
<td>BioPartners</td>
<td>Human Growth Hormone</td>
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<td>Omnitrope</td>
<td>Sandoz</td>
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<tr>
<td>Eprex (epoetin alpha)</td>
<td>Johnson &amp; Johnson</td>
<td>Binocrit (epoetin alpha)</td>
<td>Sandoz</td>
<td>Control of erythropoiesis</td>
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<td></td>
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<td>Retacrit (epoetin zeta)</td>
<td>Hospira UK</td>
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<td>Neupogen (filgrastim)</td>
<td>Amgen</td>
<td>Tevagrastim</td>
<td>Teva Generics</td>
<td>Granulocyte colony-stimulating factor</td>
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<td>Filgrastim Hexal</td>
<td>Hexal AG</td>
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</tbody>
</table>
Figure 4 – Schematic of Drug Development Process

**Discovery & Pre-Clinical Studies:**
- 3-6 years

**Clinical Studies:**
- 6-7 years

**Regulatory Review:**
- 0.5-2 years

**Post-Marketing Surveillance:**
- Lifetime of drug

- **Synthesis and Purification**
  - Animal testing:
    - Short-term
    - Long-term
  - 5,000 - 10,000 NCEs
  - 250 NCEs
  - 5-10 NCEs

- **Drug Synthesis and Purification**
  - Animal testing:
  - Short-term
  - Long-term

- **IND submission to FDA (US) or EU Regulator**

- **Registration:**
  - NDA/BLA submission to FDA
  - MAA submission to EU Regulator

- **Approval granted by regulator. Marketing begins**

- **Generally:**
  - 1-2 Approved drugs

- **Generic Drug**

**Generics:**
- ANDA submission to FDA
- Generic MAA in EU.

**Industry Time**

**Regulator & Industry Time**

**Post-Marketing Surveillance:**
- Lifetime of drug

**Phase 1 Trials**

**Phase 2 Trials**

**Phase 3 Trials**

**Phase 4 Trials**
Figure 5: Market Shares (By Volume) of Generic Medicines in Europe in 2006

(reproduced with permission from the European Generic Medicines Association)
Chapter 2

Critical appraisal of the literature on stakeholder perceptions of generic medicines – a systematic review.
Critical Appraisal of Literature on Stakeholder Perceptions of Generic Medicines.

Objective:
To provide a critical appraisal of the literature on stakeholder perspectives on generic medicines.

Methodology:
Scope
Literature published between 2003 and January 2014, which is indexed in PubMed and SCOPUS, on the topic of opinions of physicians, pharmacists and patients with respect to generic medicines.

Systematic approach to finding appropriate literature
Searches were performed in PubMed and SCOPUS in January 2014 for articles published on the topic of perceptions/opinions/behaviours/views etc. relating to generic medicines amongst the specific stakeholder groups of: general practitioners, pharmacists and patients. While interview-based studies were preferred (as that was the approach taken for the research undertaken in this thesis), any study methodology leading to a publication within the scope of this review was included. Any papers that were not published in English were excluded.

Search methodology
Searches were undertaken in PubMed using the advanced search option. Title and abstract fields were searched for publications containing the words: generic,
perception, opinion, attitude or view, along with the modifiers for each stakeholder group. For the patient group both ‘patient’ and ‘consumer’ were searched for; for the pharmacist group the word ‘pharmacist’ was used and for the physician group both ‘physician’ and ‘general practitioner’ or ‘GP’ were the terms used. Boolean operators were used to combine search components and truncation was used with the stakeholder search terms, to capture as many search results as possible. MeSH (Medical Subject Heading) terms were made use of where applicable.

Critical appraisal and synthesis

While no papers were excluded based on a subjective assessment of the quality of the reports – as per criteria described in the journal Nature Clinical Practice [1] (specifically, the recommended criteria include: relevance of the paper to the topic; whether the paper contributes new knowledge; type of research questions being asked; whether the study design is appropriate; has the potential for bias been addressed; was the study completed as per protocol; did the study test a stated hypothesis; was the statistical analysis appropriate; do the data justify the conclusions drawn; and has potential conflict of interest been identified) and the Critical Appraisal Skills Programme (CASP) checklist [2] emphasis was placed broadly on what the key results were, whether the results were valid, and whether they were relevant to the topic of stakeholder perceptions of generic medicines.

Data were extracted from the included articles and patient, physician and pharmacist perspectives defined as first-order constructs and the author’s interpretations of these constructs defined as second-order constructs.
Search Results

The PUBMED search returned the greatest number of publications. The physician/general practitioner search returned 276 articles; the patient/consumer search returned 602 articles and the pharmacist search returned 90 articles. The headings and abstracts of those 968 publications were reviewed to determine which were within the scope of this review. Figure 1 shows the approach taken and the numbers of publications obtained. The exclusion of papers was on the basis of reading their titles and abstracts and the subsequent determination that their content was not relevant to this chapter. In other words, despite the fact that the search of PUBMED may have identified these papers based on the search terms used, they were in fact not closely-enough related to the focus of this work (i.e. stakeholder perceptions of generic medicines) to warrant undergoing any appraisal beyond this. The fact that such papers were identified is a function of the design of the searches, using the selected search terms, in a deliberate attempt to “capture” as many published papers in this field as was possible.

The SCOPUS searches proved less successful; returning 280 articles relevant to patients, 138 relevant to physicians and 70 relating to pharmacists. These results comprised only publications identified in the PUBMED searches while failing to identify many and did not add any new publications. Additional applicable papers were included if referenced in those found in the above-described searches. All of the remaining articles were subjected to critical appraisal and the findings presented in the review below.
Physicians / General Practitioners

Following appropriate exclusion of publications as described above, the literature search returned only nineteen publications internationally, in the last ten years, on the topic of physician perceptions of generic medicines [3-21] (six of which were not in English [6, 7, 11, 13, 17, 20]) - only seven of which were specifically related to general practitioner opinions [4, 11, 13, 14, 17, 19, 20] (four of which [11, 13, 17, 20] were not in English). Additionally, one review on the topic of physician opinions of generic medicines was found [22] and one paper showing a historical context in Ireland, dating from 1997 [23] – both of which were included. One additional article (which was cited in one of the publications found in the systematic review) was included as it was the only interview-based study that could be found on this topic - a study of GPs’ views of generic medicines by Hassali et al in Melbourne, Australia [24] based on interviews with 10 GPs.

Following determination of applicable publications, those not published in English [6, 7, 11, 13, 17, 20] were excluded. Therefore, a total of sixteen papers [3-5, 8-10, 12, 14-16, 18, 19, 21-24] were reviewed for the physician cohort.

Pharmacists

Following appropriate exclusion of publications as described above, the literature search returned ten applicable publications [18, 25-33]. No exclusions were made.

Patients

Following appropriate exclusion of publications as described above, thirty-four reports on patient/consumer opinions of generic medicines were published within the defined scope: [3, 9, 18, 26, 34-63], (five of which were not in English [34, 37, 38, 56, 61]). One additional review article on the opinions of patients was found,
and included [64], therefore thirty papers were reviewed for this cohort. No exclusions were made.

**Overall**

Some publications had dual scope (e.g. perceptions of physicians and patients), thus an overall total of fifty (50) papers were included in this systematic review (see Table 1 for details, where it can be seen that while 16 papers were found to be relevant to physicians, 10 relevant to pharmacists and 30 relevant to patients, due to overlap, the number of papers that underwent critical appraisal was 50). An appraisal of the studies is provided below.
Review of reported methodologies

The methodological approach most commonly observed in the research appraised in this review was the self-administered questionnaire or survey, where dissemination either by post or online methods appeared to be the most frequent routes of questionnaire provision to participants. The conducting of such research by qualitative means (for example, by interview or focus group) was also identified, albeit that such reports were found in smaller numbers.

It is notable that the only physician-specific qualitative research paper that could be found was a study of GPs’ views in Australia [24] - which described the outcome of interviews with 10 participants. In the case of pharmacists, only one specifically interview-based study could be found: 16 participants were interviewed for a study in Sweden [27]. Whereas for research into patient views, five interview-based studies of the opinions of patients were found from: Iraq [51], The Netherlands [42] Norway [39, 48], and Ireland [60] (which interviewed 14, 106, 83, 174 and 42 participants, respectively). Four focus group studies from South Africa [47], the United States [54, 59], and Australia [46] (which had 73, 30, 50 and 104 participants, respectively) were found. Additionally, one mixed-subject qualitative study, which conducted focus groups with 73 consumers and semi-structured interviews with 15 healthcare professionals (six each of which were physicians and pharmacists), compared consumers’ and professionals’ opinions along with in vitro testing of a small number of generic formulations in South Africa [18].

In summary, the greatest numbers of studies found were quantitative assessments focused on the patient/consumer cohort. As is often found in
quantitative studies, the number of participants was comparatively higher than in the qualitative studies of patient and both professional groups. However, when viewed collectively, the complementary methodologies employed by the various research groups have provided a reasonable breadth and depth of insight into the patient, physician and pharmacist subject groups; albeit with a scarcity of knowledge regarding perceptions, opinions and behaviours towards generic medicines in Ireland.
Review of stakeholder opinions

Physicians / General Practitioners

One of the articles found was a comprehensive and clearly presented narrative review, by Hassali et al [22], that collated international studies published between 1980 and 2008 and coalesced the collective views of physicians as: accepting of generic substitution (GS) under policy and economic pressures but having concerns regarding generic drugs’ overall quality, reliability and switchability. This review further theorised that those concerns may prevent full adoption of generic drug prescribing and substitution by physicians, which could lead to escalation in health-care costs for governments, insurers or consumers directly [22].

This critical appraisal has gone further and has developed second-order constructs from the 16 included articles. During the appraisal process, it became clear that the articles could be defined as belonging to seven specific, non-mutually exclusive groups related to: a) physician reservations regarding generic medicines [15, 16, 18, 19, 21, 23, 24]; b) physicians’ confidence in their level of knowledge and understanding of generic medicines and associated topics [3-5, 10, 12, 18, 24]; c) reference by physicians to use of pharmaceutical industry source of information regarding generic medicines [4, 5, 8, 14, 16, 19, 23, 24]; d) physicians’ perceived influence of the pharmaceutical industry and company representatives [4, 5, 8, 9, 12, 14, 16, 18, 19, 21, 24]; e) physicians’ experience of financial incentives provided to physicians to influence prescribing behaviour [8, 12, 18, 19, 21, 24]; f) physicians’ experience of pressure applied by patients regarding branded products [4, 5, 8, 12, 16, 18]; g) physician belief that education
(specifically regarding aspects of bioequivalence) is required for greater use of generics in their market (all papers). This classification emerged only as part of this appraisal; it was not commonly used before then by authors of any of the individual articles or in the aforementioned review by Hassali et al. More specifically, with respect to a) above, in the studies describing reservations expressed by physicians (and other healthcare professionals), specific references were made to: lack of confidence in foreign manufacturers, particularly those in India and China; doubts about equivalence and the expression of personal preference for branded medications if required for themselves.

Other, less common attitudes expressed related to: physicians reporting breakthrough seizures associated with GS of an AED and as a result many are likely to prefer that generic AEDs are not used. Significant proportions of physicians express a preference for brand name medications both generally and in the case of some specific medications (in this instance, warfarin). The most recent paper on GP perceptions of generic medicines in Ireland, from 1997, stated that a majority of prescribers had concerns about the reliability and quality of generics. Also, older physicians are more likely to have a poorer opinion of generics, however despite these stated misgivings, a majority of physicians are largely accepting of the use of generic medicines. It was notable that trepidation on the part of physicians regarding potential litigation following adverse events associated with generic medicine prescribing was mentioned solely in the Irish study.

While some physicians have expressed an expectation that generics should be cheaper than they are, many state the lower cost of generics (and a
consideration of the patient’s ability to pay) as one of the main factors affecting their prescription of these medicines [10, 18, 19]. Other factors affecting use include: knowledge and reliability of the manufacturer [18, 19] and the illness being treated [21].

All of the studies appraised were included based on a subjective assessment of their applicability to the topic, using the criteria outlined earlier. It was further thought that, given the low numbers of studies available, an inclusive approach would lead to a greater chance of capturing all potential relevant perspectives. Given the paucity of literature on the topic of physician attitudes towards generic medicines, it is unsurprising that each of the papers contributes some new information, albeit specific to particular countries or regions (Table 1) and, as such, the published outcomes may not be readily generalizable. It is also notable that with relatively few exceptions [8, 12, 14, 18, 23, 24] the researchers utilised questionnaires comprised of closed questions, many of which relied on Likert scale-type responses. Of the remainder, only one study [18] makes use of focus groups and explores supply-side challenges associated with poor quality of generic medicines; while semi-structured interviews were used in the three studies that concentrated on physicians practicing in areas with high levels of poverty and low generic medicine market penetration [8, 12, 14]. In almost all cases, the study instruments were assessed for face validity and pilot tested. However, only one of the papers reported specific efforts to ensure appropriate reading level [3], while in three studies [9, 16, 18] payment was provided to physicians participating. Indeed, in one of the studies [9], the payment considerably altered the expected response rate, acknowledged by the authors who however stated that they believed the payment did not affect the nature of
the responses provided. It was also noted that with the exception of a single study [3], no data were presented as to whether the participating physicians freely communicated their perspectives on generic medicines to their patients, a factor that may influence subsequent consumer attitudes and behaviour.

Across the 16 papers appraised, varying recruitment strategies were employed, with a number of the research groups stratifying participants albeit with a wide range of response rates. However, recruitment biases were evident in a subset of these [3, 9, 10, 12, 14, 19, 23], with the most challenging bias involving recruitment of participants based on databases of suitable practitioners provided by representatives of the pharmaceutical industry [14]. Focusing specifically on the Irish report [23], the authors reported a potential bias based on attendance by a majority of respondents at generic medicine information events hosted by the pharmaceutical industry.

On a positive note, one study assessing the attitudes and underlying rationales of psychiatrists towards generic products [21] deserves mention. The authors, recognising a potential bias risk associated with the fact that all participants were attendees at a single conference, established elaborate vignette-based scenarios, with multiple potential questioning delivered to a large number of participants enabled further by sophisticated statistical analyses.
**Pharmacists**

While assessments of pharmacist perceptions of generic medicines have been carried out in a relatively limited number of other countries, in the past 10 years: New Zealand [30], Portugal [26], South Africa [18], Malaysia [29], France [31] and Sweden [27] – and also in relation to specific medications such as antiepileptic formulations [28] and inhalers [25] – this literature search did not return any peer-reviewed publications on the topic of pharmacist perceptions of generic medicines in Ireland. In fact, as the ten studies found appear to be the only published investigations on the topic of pharmacist perception of generic medicines – this appears to be a relatively underexplored area, internationally.

While critically appraising the papers found, and attempting a synthesis of their findings, it was evident that, compared to the physician-focused reports critiqued above, there was considerably less consensus regarding potential second order constructs. To interpret, present and discuss the findings of the papers, the chosen approach was to identify synthetic unifying themes (an approach described by Fleming [65]). The four unifying themes identified, comprised of sub-themes or issues, are detailed in Table 2. The themes are:

- **Pharmacists’ concerns regarding patient understanding of generic medicines and substitution, patient safety and compliance with treatments** (7/10 papers)
- **Pharmacists’ understanding of generic medicines and substitution, and pharmacists’ confidence in quality, efficacy and safety of generic medicines** (6/10 papers)
• Practical aspects of pharmacists’ practice as affected by generic medicines and substitution (9/10 papers)

• Pharmacists’ suggestions to improve generic medicines use and education of stakeholders regarding this (9/10 papers)

Interpreting these perspectives, it appears that while pharmacists tend to hold mainly positive views of generics with respect to their safety and equivalence and support for GS (e.g., German pharmacists overwhelmingly cautious [25] while the French counterparts were mainly positive [31]), for some pharmacists there remains cause for concern [18, 25, 29, 30]. Of these, one of the primary concerns relates to patient safety and, explicitly, the potential for confusion to be caused, particularly in the case of elderly patients, due to differing appearance and presentations of generic medicines, which has been reported to have an impact on medication compliance [25, 27]. In fact, two suggestions made by pharmacists to potentially mitigate risk in this area were a) that patients be informed and involved in the decision-making process regarding the selection of medicinal products provided to them [25] and, b) that an upper age limit be established such that older patients (possibly more prone to confusion) would not encounter unfamiliar medications [27].

Many of the studies reported an increased pharmacist workload associated with generic medicines, including provision of generic medicine-related information to patients and variations in stock management. Possibly related to these pragmatic topics, almost all of the papers stated pharmacists’ recommendations for increased stakeholder education regarding generic medicines and substitution. Further, in one study addressing both patient and pharmacist perspectives, 78% of patients believed themselves well-informed regarding
generic medicines while 83% of their pharmacists perceived a lack of patient understanding [26]. However, notably, recommendations regarding education are not all focused on patients and include measures be taken to ensure that the pharmacist group have the correct knowledge in order to aid and facilitate this knowledge transfer to patients [18, 27, 29-31, 50]. That said, some pharmacists believe that advice given to patients, by pharmacists, regarding their medications is less valued or trusted than advice from prescribing physicians [26, 27].

Each of these ten papers represented efforts made to elucidate the views and behaviours of pharmacists. Given the general scarcity of information regarding perceptions of this stakeholder group, they each make a contribution to this field of interest. As shown in Table 2, most of the research groups involved made efforts to design their study instruments based on key opinion leader advice and, in the majority of cases, the instruments were piloted before use. However, 7 of the 10 papers failed to protect against recruitment bias, with one dominated by pharmacy owners who may be influenced by profit margins achievable through dispensing originator medicines and attractive industry bonusing / reimbursement [29]. Another (originating from South Africa) [16] described an assessment in which both perceptions and experience of generic medicine quality in South Africa were compared with actual generic medicine quality. Given the relatively poor reputation of generic medicine manufacture in South Africa (as stated in the paper itself), the outcomes were predictable and did not add any new information to the field in that context. The transferability of the study outcomes beyond South Africa is further hampered by the authors’ acknowledgement that due to their purposeful sampling in urban (affluent) areas
of South Africa, their results may be confounded by additional negative biases attributable to those particular communities and population demographic. While other papers also focus on specific population groups or countries, it is the combination of attitudinal perspectives with evaluation of experience of actual specific defined products that limits transferability in this case.

One criticism is possible of almost all of the papers appraised in that they focus on the negative connotations of generic medicines as experienced by pharmacists whereby only one study [26] reported incidence (albeit low) of patients requesting generic medicines rather than the more frequently reported reticence of patients. It would be interesting to meter such incidence as recorded or perceived by pharmacists and to compare those data with patient-reported measures. A final comment relates to a possible “missed opportunity” throughout these studies, whereby study instruments have explored pharmacists perceptions and experiences of generic medicine efficacy, safety and quality but only 2 of the 10 studies followed this line of thought by determining what actions the pharmacists then took with respect to adverse event reporting, an important facet of pharmaceutical regulation that relies on post-market monitoring of products (originator or generic) to ensure that patient safety is assured.

Patients

Patient-focused studies have, relative to the opinions of healthcare professionals, had comparatively more attention, internationally. In summary, published reports have originated in Norway (patients attitudes to generic substitution) [36], Finland (preferences of patients for generic and branded OTC (over-the-counter) pain medicines) [40], Portugal (patient perceptions of underuse of generics and their attitudes towards generic substitution) [26], South Africa
(consumer perceptions of generic drug quality compared with actual drug quality) [18, 47], New Zealand (patients' perceptions, knowledge and attitudes regarding generic medicines and investigation of patients' attitudes towards generic substitution of oral antipsychotics) [42, 45], Iraq (consumers' knowledge relating to generic medicines) [51], the United States (patient knowledge of, and attitudes relating to, formulation switching of antiepileptic drugs) [28], and Ireland (patient perceptions of generic medicines) [60], amongst others.

In critically appraising the papers found, and attempting a synthesis of their findings, it was evident that, compared to the pharmacist-focused reports critiqued above, there was greater consensus regarding potential second order constructs. To interpret, present and discuss the findings of the papers, the chosen approach was to identify synthetic unifying themes [65]. The unifying themes identified, comprised of sub-themes, are detailed in Table 3. The themes are:

- Patients' lack of confidence in generic medicines, contributed to by initial scepticism, provision of poor or poorly understood information, and concerns regarding packaging and/or appearance of generic medicines (18/30 papers).
- Patients actual experiences in using generic medicines, not exclusively negative, including difficulties associated with treatment adherence or compliance (9/30 papers).
- Factors influencing patient acceptance of generic medicines, including patient involvement in decision-making, age, income and severity of illness (7/30 papers).
Provision of information and education regarding generic medicines (10/30 papers).

In a 2009 review article on patient views of generic medicines (reviewing literature up to October 2008), Hassali et al [64] determined that patient confidence and knowledge had improved steadily since the 1970’s, with the greatest levels of acceptance being seen in developed countries. This growth in confidence was ascribed to mass educational efforts and greater communication amongst healthcare professionals and patients - although safety and efficacy were stated as being the main barriers to acceptance of generic substitutions. Hassali et al stated that consumers with lower educational levels tend to have greater mistrust in generics, and this appears to continue to be the case, as reported in more recent research [26, 39, 45]. Interestingly, however, this did not appear to be the case in a study published by Kohli & Buller in 2013, who stated that even though their study population had lower socioeconomic status and education, more than half of respondents reported choosing generic drugs rather than brand name drugs [62]. When delved into more deeply, the apparent disparity is somewhat explained by the fact that while the latter study is broadly similar to the other three detailed above with regard to methodology and number of participants, the focus is solely on generic over-the-counter (OTC) medicines. In fact, the authors found that, similar to the Finnish study above (which was inclusive of OTC medicines), lower cost and number of doses in the package were important factors that respondents rated as having substantial influence on their purchase of generic OTCs. In addition, factors that were determined to have no statistical significance in influencing consumer purchasing patterns included advice from healthcare provider, advice from family and friends, look of the
package, degree of sickness (mild), taste of the OTC, and greater effectiveness of the OTC. It is noteworthy though that the authors did not survey participants about their health insurance status and whether they received coverage for OTC medications.

The authors of the 2009 review recommended that further research in the area of patient views should be focussed on developing countries, where cost savings are more urgently needed; and in fact research published since 2009 has been more focussed on developed countries, possibly as a result of where research funding is available to investigate consumer opinions.

The greatest level of poor opinion and mistrust in generics is seen in the patient rather than healthcare professional cohort. They report negative perceptions in general as well as in specific terms. In general terms, views are reported such as: being largely unwilling to accept, or having mistrust in generics [46, 52]; having had negative experiences following a generic substitution [36, 48]; mistrust of foreign manufacturers [46] and a belief that cheaper equals inferior [35, 60]. In specific terms patients reported breakthrough seizures following substitution of an antiepileptic drug (AED) [9, 41, 57, 63]; reported being advised by a physician not to accept GS for an AED R61 and are of the opinion that poor people are forced to ‘settle’ for generics [35, 54] (in one study nearly half of the respondents stated that they would refuse a GS if it was only to have the health system money [55]). This reported behaviour is supported by beliefs that generic medicines are believed to be poor quality, are treated with suspicion and are considered ‘second class’ within this cohort [42, 47, 60].
Many patients do not consider generic medicines equivalent to the branded product [36, 39, 46, 48, 54, 55] and there is also a belief that brand name medications are more effective/potent and have fewer side effects [39, 48, 53, 54]. Furthermore, patients appear to be more accepting of generics for treatment of minor illnesses but prefer branded medicines for more serious health problems [45, 54, 57, 59]. Links between GS and lack of compliance with taking medication can also be observed: patients have reported that GS made it more demanding to keep track of their medication [39, 48] and that variability in packing or appearance caused issues [46, 60]. Worryingly, in one study patients were seen to be taking two or more equivalent medications, concurrently, due to lack of understanding, following a GS [48]. While many misconceptions are held within the patient group [45], one particularly disturbing association can be observed in the literature: some consumers hold the belief that generic and falsified (that is, counterfeit) medicines are the same [18, 48].

There are, however, several studies that report positive views in the patient group. In a Finnish study a majority of patients indicated that they did not notice any difference following a GS [49]. Other studies have shown patient groups that don’t consider generics to pose a safety risk [44, 49, 60]; that they generally accept generics as being equivalent [59] and in one study only a minority believed that brand name medicines were better than generics [44]. While perceptions appear to be improving over time [44], recent literature in the area of patient perceptions has a common recommendation running through it: the continued need for effective information to be communicated to consumers and for trusted healthcare professionals to take time to provide clear education about the equivalence of generic formulations [18, 26, 36, 39, 44, 53, 54, 60]. Knowledge
gaps, often considerable, exist within this cohort [50, 51, 54, 60]; hence education is seen as a key factor to improvement of confidence in, and therefore usage of, generic medication. In support of this, one study found that the provision of a short explanation was seen to have a positive effect on patient likelihood to accept a generic [42]. Whether accepting or not, patients wish to be informed as to their healthcare matters – with a view amongst patients that a GS should not take place without their being informed [41, 60].

While the lower cost of generics is the primary incentive associated with their use [26, 36, 40, 49, 51, 62] it is interesting that an awareness of the benefits of generics does not always translate into a preference for their use [52, 53]. Indeed, a study in Finland [49] showed that while a majority of patients stated that more generics should be used, they did not exhibit a preference to use them themselves.

There appears to be considerable evidence that patients who have had a previous good experience with a generic medication are more likely to accept generics in the future [18, 26, 43, 45, 50, 58] and, as patients who have never experienced a GS appeared to be more concerned about taking a generic than those who had [57], this reinforces the importance of the role of healthcare professionals, and of provision of accessible information, to the patient cohort. In fact, several studies have reported patient trust in healthcare professionals, and their acceptance of recommendations of generic medicines, by trusted professionals, despite their own lack of confidence in GS [26, 42, 47, 49-51, 60].

In critically appraising these thirty studies, particular attention was paid to the
quality of the study design, the analysis and interpretation of the data as described by the authors, and to the conclusions drawn. A number of potential confounding factors were evident:

- In the majority of the studies, there was an apparent bias towards investigating negative connotations of patient perceptions of generic medicines. Only a subset of the studies investigated the positive experiences of patients, and whether they had preferences for or had habitually requested generic medicines over originator products [42, 44, 50, 53, 57, 59, 62, 63]. In one specific case, data are presented only for patients who had declined recommended generic medicines [52].

- In determining attitudes and perceptions of patients, many of the studies relied on self-reported questionnaires. In doing so, there is an assumption made that the information provided by the patients regarding their exposure to generic products and, indeed, their stated illnesses are factual. Only four of the research groups correlated patient-derived information with patient records [43, 54, 55, 58].

- In almost all cases, the authors failed to comment on the potential impact of incomplete/non-returned questionnaires and the information that they may have provided. However, in one specific case, an assumption is made that non-return of data equated to dissatisfaction with generic medicines, leading to a statement that a third of patients held that view [35]. This is problematic, as the missing data corresponded to almost 50% of the “dissatisfied” cohort. The researchers would have been more accurate in stating that “…approximately one sixth of patients explicitly stated dissatisfaction”.

- Many of the studies use convenience samples raising a query regarding
the generalizability of the results to the specific population being evaluated, indeed transferability of much of the data are hampered by a lack of information regarding participant socioeconomic status and educational background. Similarly, many of the studies focus on narrowly-defined cohorts such as those on specific medications (e.g., anti-hypertensive, anti-epilepsy) or culturally-discrete communities (e.g., emigrant Pakistanis in Norway, post-apartheid elderly patients in South Africa, or poorly-educated black females in rural area of southern states of the USA).

- Validity is questionable in reports with low response rates (e.g., 6% [63])
- Payment for participation is recorded in two papers, with some indication that the responses obtained from participants may have been different from those expected, possibly due to wishing to provide perceived acceptable answers [54, 59] and,

- Especially pertinent to the context of this thesis, almost all of the studies failed to take into consideration survey readability (for example: Flesch Reading Ease or Flesch-Kincaid Grade Level assessments) and the influence of that on participant responses.
Discussion

There are no systematic reviews in the literature that describe the perceptions of pharmacists, and this review is the first (to the author’s knowledge) to include the views of all three of the main cohorts in generic medicines usage (that being: prescribers, dispensers and consumers). Quantitative studies have been the main approach taken in determining the views and behaviours of the cohorts in the past. These are generally in the form of self-administered questionnaires/surveys, either online or by post. Qualitative studies [18, 27, 48, 51, 54, 59, 60] were also identified, albeit that such reports were found in smaller numbers (only 7 of the 50 publications made use of qualitative methods). These studies have made a significant contribution, however in showing, for example, that providing patients with a short explanation about generic medicines had a significantly positive effect on their willingness to take them [42]. Reinforcing the perception that there remains a need for information provision and education, for example, one qualitative study referred to in this review has shown that correct understanding of generic medicines by the general public – as determined by previous quantitative, survey-based studies – may be overestimated (i.e., confusion in the patient cohort between the words ‘generic’ and ‘genetic’,) [60].

However, irrespective of choice of qualitative or quantitative approach, similar trends in opinions and beliefs held have been reported.

In all three stakeholder groups, opinions of generic medicines have improved over the years but some mistrust remains – most particularly in the patient group. The physician group shows some level of lack of confidence, although not
as much as consumers. Pharmacists exhibit the greatest degree of positive opinion, and acceptance of, generic medicines.

There tends to be agreement that provision of education – particularly, but not exclusively, to the patient cohort – is one of the key factors to improving confidence in, and hence usage of, generic medications. A common finding is that acceptance of generics appears to be higher in consumers with higher levels of education [26, 45], and patients from lower socioeconomic demographics, hence having lower levels of education, tend to have greater mistrust of generics [64], with the exception of the findings of Kohli & Buller in 2013 [62], discussed earlier. However, there may be some bias amongst researchers in focusing on negative connotations while disregarding the equally-interesting area of patient acceptance and even, possibly, preference for generic medicines. Indeed, when investigated, positive attitudes were seen to arise due to good experiences with generic medicine use or for economic reasons.

There appears to be a strongly held belief, particularly in the patient group, that less expensive equals lower quality [36, 53, 60] – reinforcing the need for ‘myth-busting’ education. While consumers may hold that opinion due to experience with other consumer products, the same principles do not apply to pharmaceuticals due to the highly regulated nature of medicines manufacture and marketing approval requirements. Provision of education on these topics to both consumers and physicians (who have exhibited a lack of knowledge in the regulation of medicines in some publications [4, 19, 22]) could be instrumental to improving confidence in generics by providing greater understanding as to why, in the case of generic medicines, lower prices do not equate with poorer levels of quality or efficacy. However, it is interesting that while patients value the
opinions of, and information provided to them by, physicians and pharmacists, there is some patient preference for physician-sourced guidance (e.g., in South Africa [47]) which is a factor also commented on by some pharmacists (see earlier notes).

Of potential importance to policy makers is the on-going trend – reported in the 2009 review [64] and again in a 2013 study [62] that positive attitudes towards generics amongst the consumer group do not necessarily translate into increased usage of generic products.

While acknowledging the fact that very few studies will be perfect in both design and completion, and that contingencies in implementation of study protocols can mar any project, the critical appraisal of the studies included here highlights some points that may confound or limit the data they generated, all of which are discussed at length in the appropriate earlier sections. In summary, however, some of the physician-oriented papers involved recruitment biases, the most notable of which were due to use of pharmaceutical industry-derived databases for participant selection [14] and payment to physicians for their inclusion in studies [9, 16, 18]. With respect to pharmacist-oriented papers, there were again recruitment biases in some reports, mainly due to relatively limited geographic distribution of participants, and a potentially-dominant focus on reporting negative connotations of generic medicines while, arguably, missing opportunities to report and discuss positive attributes of generic medicines and substitution from the pharmacist perspective. Given that this appraisal involved comparatively greater numbers of patient-focused studies than those featuring perceptions of other stakeholders, it is perhaps reasonable that the greatest number of confounders were determined in the larger collection. Specifically, in
the majority of the studies, there was an apparent bias towards investigating negative connotations of patient perceptions of generic medicines. Validity, transferability, participant selection and understandability of the study instruments used have also been discussed in earlier sections, and may in some way challenge the outcomes of the studies. However, it must be acknowledged that in most of the studies appraised, the authors attempted to understand these factors and how they may have influenced their data generation, analysis and interpretation of outcomes.

**Recommendations**

Further research may be needed in the area of pharmacist opinions as they have a direct impact on patient acceptance of generic medication and, relative to the other two cohorts, very little attention has been paid to this group.

More research in the area of equivalence of generic medicines – either to support or amend regulatory bioequivalence requirements – would be a positive step, as some discrepancy exists between patient and professional experiences and the stated equivalence by regulators [15]. This appears to be particularly necessary in the area of AEDs [9, 63].

While many misconceptions are held within the patient group [45], a disturbing association can be observed in the literature regarding patient belief that generic and falsified (that is, counterfeit) medicines are the same [18, 48]. Given that generics are fully authorized, off-patent versions of branded medications, and very different from falsified medicines, this indicates that any educational interventions focused on this cohort need to include at least some information
that explains the difference between generic and falsified medicines in order to remove this falsely held belief as a source of mistrust of generics.

As several publications report that a previously positive experience with a generic medicine is more likely to improve patients’ positive opinions of, and confidence in, generic medicines [18, 43, 45, 58]—combined with the influence and trust which patients demonstrate in physicians [26, 60]—it is arguable that if physicians (and pharmacists) spend time explaining the equivalence of generic medication to a patient at their first encounter, this will encourage use of the generics and, therefore, improve future use of generic medications by that consumer.

**Limitations**

This review was limited in that PubMed and SCOPUS were the only databases used for sourcing literature (however, PUBMED and SCOPUS combined represent considerable coverage of reputable journals) and that articles not published in English were excluded from the scope of this review.

In this review, there was a balance achieved between the sensitivity of the searches (i.e., the capture of as many relevant papers as possible) versus the specificity (i.e., whereby screening of very large numbers of papers would be required to identify those relevant to the focus of this review). These results, whereby PUBMED proved more effective in identifying relevant publications than did SCOPUS, mirror results seen by Freeman *et al* [66] who reported that PubMed proved more specific than Google Scholar in locating relevant primary literature when comparing effective search databases for drug-related topics.

Furthermore, Falagas *et al* [67] reported that the keyword search with PubMed
offers optimal update frequency and includes online early articles although SCOPUS offers more coverage of journals. PubMed, however, remained an optimal tool in biomedical electronic research [67].

For qualitative reports, impact of the intricacies of the relevant social contexts, methodologies (i.e., participant observation, ethnography, interviews, focus groups, textural or conversational) was not delved into beyond determining whether represented biases detrimental to the findings of the studies. Recognizing that there has been a historical difficulty in including qualitative research easily into systematic review methodologies [68], considerable emphasis has been placed on assessing each of the reports included here using criteria for assessment of qualitative research promoted by the British Medical Journal [69] and Letts et al [70]. In doing so, instead of detailing each aspect of each paper, the focus has been placed on the believability, robustness and transferability of the studies. Beyond that, therefore, there is a presumed credibility with respect to the researchers involved, reinforced to a great extent by the cumulative validation attributable due to the clear alignment of individual studies with one another and the triangulation with data presented in the quantitative papers.

With respect to quantitative studies, the questions of whether the cohorts of subjects were (statistically or demographically) representative of their target communities was critiqued. Where elements of any paper were found to be weak in this regard, this has been detailed in the text above.

**Conclusion**

While acceptance of generic medications is improving over the years, substantial mistrust and lack of confidence remains – particularly within the patient and physician groups. A key factor in improving the confidence of these cohorts is the
provision of information and education – particularly in the areas of equivalency, 
regulation and in dispelling myths about generic medicines (such as the belief 
that they are counterfeits). Moreover, as patient trust in their physician often 
overrules their personal mistrust of generic medicines, improving the opinions of 
generics within the physician cohort may be of critical importance to improve 
usage and acceptance of generic medicines in the future. Given that reports 
indicate that patients who have a positive initial experience with a generic are 
more likely to maintain a positive opinion into the future, the physician-patient 
relationship and interaction may be key to influencing improving patient 
approval of generic medicines. To substantiate this facet of generic medicines, it 
may be useful for all stakeholders were a Cochrane review to be completed in this 
area; as of July 2014 a search of the Cochrane Database of Systematic Reviews 
found that no Cochrane Review has been published and no protocol title 
registered focused on patient, pharmacist and physician perspective on generic 
medicines (with reference to Cochrane’s Primary Health Care, Health Care of 
Older People and Effective Practice and Organisation of Care groups). Future 
work could target this area.
References:


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qualitative research? A critical perspective. *Qualitative Research* 2006, 6(1):27-44.


Table 1: Summary of studies (sorted by reference number)

<table>
<thead>
<tr>
<th>Setting/location</th>
<th>Subject(s)</th>
<th>n</th>
<th>Type</th>
<th>Focus</th>
<th>Main findings</th>
<th>Ref</th>
</tr>
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<tbody>
<tr>
<td>Canada</td>
<td>Patients &amp; physicians</td>
<td>81 patients &amp; 110 physicians</td>
<td>Questionnaire</td>
<td>Interchangeability of warfarin</td>
<td>While most patients and physicians appear to have accepted the principle of therapeutic equivalence of generic and brand-name warfarin, a sizable minority has concerns that could influence prescribing and compliance – believing that generic warfarin was neither as safe nor as effective as brand-name warfarin. Forty-four per cent of physicians agreed or strongly agreed that they would rather prescribe brand-name than generic warfarin for patients starting warfarin therapy. 19.4% of physicians who had switched patients from brand-name to generic warfarin actually reported difficulties in managing the switch.</td>
<td>[3]</td>
</tr>
<tr>
<td>Slovenia</td>
<td>GPs</td>
<td>117</td>
<td>Postal survey</td>
<td>Attitudes, generic prescribing</td>
<td>The majority of GPs (88.9%) perceived generics to have the same effectiveness as branded drugs. One quarter of GPs would prescribe more generics if additional clinical trials were presented. 37.3% would follow advice of academic detailers and 30.3% expected the generics to be even cheaper than they were. Independent detailing was welcomed by 63.8% of GPs because of the big influence of the pharmaceutical industry on the prescribing habits. 15.5% thought that the industry had a tremendous impact on their prescribing habits.</td>
<td>[4]</td>
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<tr>
<td>Saudi Arabia</td>
<td>Physicians</td>
<td>772</td>
<td>Questionnaire</td>
<td>Perceptions and attitudes, generic prescribing.</td>
<td>Most physicians (79%) support generic substitution, but they indicated that there are certain clinical situations where they prefer to use brand name drugs. Physicians reported receiving visits and samples more frequently from representatives of brand name companies. Physicians did not report a significant difference in pressure from patients to prescribe either generic or brand drugs. Most physicians had a positive attitude towards the government role in assuring the quality of local drug products (80%) and in enforcing physicians to prescribe generic drugs (85%).</td>
<td>[5]</td>
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<tr>
<td>Greece</td>
<td>Physicians</td>
<td>1204</td>
<td>Postal questionnaire</td>
<td>Perceptions</td>
<td>Physicians seem to be open to prescribing generic medicines despite the fact that they did not do so at the time the article was published. The expansion of the generics market should have a positive impact on patients’ access to cheaper drugs.</td>
<td>[8]</td>
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<tr>
<td>USA</td>
<td>Patients &amp; physicians</td>
<td>550</td>
<td>Online Survey</td>
<td>Perceptions in the context of treatment of epilepsy</td>
<td>Two-thirds of physicians and 34% of patients have linked breakthrough seizures to generic AED substitution. Physicians (75%) and patients (65%) were also concerned about efficacy. About half of physicians were extremely/very likely to request that brand AEDs not be substituted with a generic.</td>
<td>[9]</td>
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<tr>
<td>Jamaica</td>
<td>Physicians</td>
<td>60</td>
<td>Questionnaire</td>
<td>Acceptance, perceptions</td>
<td>Perceptions among physicians and patients do not align with the FDA position that generic AEDs have the same clinical effect and safety profile as branded AEDs. More research is needed to determine if generic AEDs are bio-equivalent in real-life situations.</td>
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<tr>
<td>Pakistan</td>
<td>GPs</td>
<td>206</td>
<td>Questionnaire</td>
<td>Perceptions, attitudes</td>
<td>Close to three quarters of the respondents (71.8%) showed correct knowledge about generic medicines being a ‘copy of the brand name medicines’ and ‘interchangeable with brand name medicines’ (71.8%). In terms of safety, the majority of respondents (41.26%) incorrectly understood that the generic medicines are less safe than brand name medicines. The total percentage of correct responses was seen in 53% of the respondents. More than half of the respondents agreed that locally manufactured medicines are of the same effectiveness as brand name medicines (55.4%). The Majority of respondents believed that their prescribing decision is influenced by pharmaceutical company representatives (n=117; 56.8%). More than three-quarters of the</td>
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respondents expressed their wish to prescribe low cost medicines in their practice (76.2%). More than one third of the respondents expressed their uneasiness to prescribe products from all local manufacturers (35%). Knowledge gaps evident.

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<tbody>
<tr>
<td>Italy</td>
<td>Family pediatricians</td>
<td>303</td>
<td>Online questionnaire</td>
<td>Perceptions, patterns of use</td>
<td>Prone to prescribe trade medicines more frequently, since only 13.5% of them declared that more than a half of their patients were treated with generic medicines. Major issues related to scepticism about reliability of bioequivalence tests and safety of switchability from branded to generic equivalents. More information about generic drugs and more research in the field of paediatric pharmacology are needed for increasing generic medicines prescription rate.</td>
<td>[15]</td>
</tr>
<tr>
<td>USA</td>
<td>Physicians</td>
<td>506</td>
<td>Questionnaire</td>
<td>Perceptions</td>
<td>A meaningful proportion of physicians expressed negative perceptions about generic medications, representing a potential barrier to generic use. Payers and policymakers trying to encourage generic use may consider educational campaigns targeting older physicians. Over 23% of physicians surveyed expressed negative perceptions about efficacy of generic drugs, almost 50% reported negative perceptions about quality of generic medications, and more than one quarter do not prefer to use generics as first-line medications for themselves or for their family. Physicians over the age of 55 years were 3.3 times more likely to report negative perceptions about generic quality.</td>
<td>[16]</td>
</tr>
<tr>
<td>South</td>
<td>Consumers</td>
<td>73</td>
<td>Focus group</td>
<td>Comparison of</td>
<td>Respondents described drug quality in relation to the</td>
<td>[18]</td>
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<tr>
<td>Africa</td>
<td>&amp; HC professionals</td>
<td>consumers &amp; 15 HC professionals</td>
<td>discussions with consumers Semi-structured interviews with HC professionals</td>
<td>HC professionals’ and consumers’ opinions along with testing of generic formulations</td>
<td>effect on symptoms. Procurement and use behaviour of healthcare providers were influenced by prior experience, manufacturers’ names and consumers’ ability to pay. Some reservations regarding quality of generics on part of HC professionals, some perceive products manufactured in India and China as being inferior. Falsified medicines impact on consumer confidence in generics. All formulations passed the in vitro tests for quality. Therefore, study showed clear differences between perceptions of quality and actual quality of medicines suggesting implementation of generic medicines policy requires information gaps to be addressed.</td>
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<tr>
<td>Malaysia</td>
<td>GPs</td>
<td>87</td>
<td>Postal survey</td>
<td>Knowledge, perceptions</td>
<td>Although it appeared that GPs have largely accepted the use of generic medicines, they still have concerns regarding the reliability and quality of such products. GPs need to be educated and reassured about generic products approval system in Malaysia concerning bioequivalence, quality, and safety. Advertisements and product bonuses offered by pharmaceutical companies, patient’s socio-economic factors as well as credibility of manufacturers were factors reported to influence their choice of medicine.</td>
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<tr>
<td>Germany</td>
<td>Physicians – psychiatrists</td>
<td>410</td>
<td>Survey</td>
<td>Decision making between generic and branded</td>
<td>Psychiatrists were more likely to choose branded drugs when imagining choosing the drug for themselves (vs. recommending a drug to a patient). Psychiatrists were more likely to choose generic antidepressants than generic antipsychotics.</td>
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<td></td>
<td>Physicians</td>
<td>14 papers 1980-2008</td>
<td>Review article</td>
<td>Views</td>
<td>Physicians lack knowledge of regulatory requirements imposed on generics. Being cheaper than their branded counterparts raised the concerns of the physicians about their quality, safety and effectiveness, especially in the presence of heavy and successful promotional activities from brand name industry. Review suggests that physicians will resist generic practices at the beginning of introducing them, but this resistance will wane in the face of policy measures and economic pressures, but not to the extent of regular generic prescribing. Although physicians accepted generic substitution under policy and economic pressures, they still have concerns about overall generic drugs’ quality and reliability, and switchability of certain drug categories, which differ from country to country. These concerns prevent the full adoption of generic drugs prescribing and substitution by physicians, which can lead to escalation in health-care costs either on the governments, insurers or consumers</td>
<td>[22]</td>
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Additional predictors for choosing a generic drug were a higher share of outpatients, less negative attitudes toward generics and higher uncertainty tolerance. Psychiatrists’ decision making in choosing between branded or generic antidepressants or antipsychotics is to a large extent influenced by vague attitudes towards properties of generics and branded drugs as well as by “non-evidence based” factors such as uncertainty tolerance.

**Ref**

- United States
- Australia
- Finland
- Malaysia
- Slovenia
- France
- Ireland
- United Kingdom
- Jamaica.
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<tr>
<td>Ireland</td>
<td>GPs</td>
<td>107</td>
<td>Postal survey</td>
<td>Views, concerns</td>
<td>Low levels of generic prescribing. Primary concerns of Irish GPs - reliability and quality. GPs were concerned that pharmacists may legally dispense more expensive branded products for private prescriptions written generically. Prescribers are interested in economic prescribing but are not being educated and reassured about generic medicines.</td>
<td>[23]</td>
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<tr>
<td>Australia</td>
<td>GPs</td>
<td>10</td>
<td>Semi-structured interview</td>
<td>Perceptions</td>
<td>Suggested some methods that could be used to increase the current rate of generics prescribing, including financial reward for GPs, patient education on generic medicines, convincing GPs of the safety and efficacy of generic medicines and educating senior medical students on issues involving generic medicines and generics prescribing. Study suggested that GPs in Melbourne have mixed attitudes to generics prescribing. Also shows that misconceptions about safety and efficacy of generic medicines still persist among some GPs and that unless they are sufficiently educated by interested parties, such as the government and the generic medicines industry, this will have a negative impact on utilisation of generic medicines in future.</td>
<td>[24]</td>
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<tr>
<td>Australia, Canada, France, Germany, and the UK</td>
<td>Pharmacists, Powder inhalers</td>
<td>254</td>
<td>Web questionnaire</td>
<td>Attitudes, interchangeability of dry inhalers</td>
<td>Just 6% of pharmacists considered that dry powder inhalers are interchangeable, with a high level of concern shown about interchangeable use. Patient confusion was the main concern, expressed by 77% of respondents.</td>
<td>[25]</td>
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<td>Pharmacists also envisaged substitution having an adverse impact on pharmacy stock levels (72%), patient device handling (70%), pharmacist workload (63%), patient compliance (56%) and outcomes for the patient (51%), with pharmacists in Germany having a particularly negative view and those in France generally the most positive. Only 22% would contact the prescribing physician often/very often for approval of the substitution. Pharmacists in Germany were particularly negative about the interchangeable use of dry powder inhalers.</td>
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<tr>
<td>Portugal</td>
<td>Patients &amp; pharmacists</td>
<td>95</td>
<td>Questionnaire</td>
<td>Perceptions, attitudes</td>
<td>More information for patients is necessary, greater levels of acceptance seen in patients with higher education levels or those who had discussed substitution with physician/pharmacist. 89% patients willing to accept generic on recommendation of HC professional. Reasons for underuse were mistrust of patients in efficacy, lack of generic prescribing, lack of information for patients. Measures targeted at physicians necessary. Policies should not rely on patients' own initiative to request GS. Patients with experience more willing to accept generics.</td>
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<td>Pharmacists</td>
<td>16</td>
<td>Interviews</td>
<td>Experiences, attitudes</td>
<td>Pharmacists found it positive that generic substitution decreases the costs for pharmaceuticals but also emphasized that the switch can confuse and worry patients, which could result in less benefit from treatment.</td>
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<tr>
<td>Malaysia</td>
<td>Pharmacists</td>
<td>219</td>
<td>Postal questionnaire</td>
<td>Views</td>
<td>Respondents claimed that generic substitution has changed the focus in the pharmacist-patient meeting towards economics and regulations. Generic substitution is not primarily an issue of generic versus brand-name products, but concerns above all the challenges that the switch implies for patients and pharmacists. To prevent known confusion and concerns among patients it is important that community pharmacists acquire the necessary tools and knowledge to manage this situation, to communicate effectively with patients.</td>
<td>[29]</td>
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<tr>
<td>New Zealand</td>
<td>Pharmacists</td>
<td>360</td>
<td>Postal questionnaire</td>
<td>Views, knowledge</td>
<td>Only 50.2% of the surveyed pharmacists agreed that all products that are approved as generic equivalents can be considered therapeutically equivalent with the innovator medicines. Majority of the pharmacists understood that a generic medicine must contain the same amount of active ingredient (84.5%) and must be in the same dosage form as the innovator brand (71.7%). About 21% of respondents though that generic medicines are of inferior quality compared to innovator medicines. Most of the pharmacists (61.6%) disagreed that generic medicines produce more side effects than innovator brand. The Malaysian pharmacists' lack information and/or trust in generic manufacturing and/or approval system in Malaysia.</td>
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<td></td>
<td>Pharmacists</td>
<td>1000</td>
<td>Postal survey</td>
<td>that generic medicines and original brand medicines are equally effective. A large number of pharmacists reported concerns regarding brand substitution and offered suggestions, such as the need for advertising campaigns, patient pamphlets, updating prescribers' software, and distinct packaging for generic medicines. About one-third of pharmacists correctly defined the term &quot;generic medicines,&quot; suggesting discrepancies in pharmacists' knowledge and perceptions of generic medicines. Concerns were raised regarding: quality, safety, and effectiveness; however, most of the pharmacists acknowledged the economic benefits to the health care system. 90% of the pharmacists were favourable to the implementation of GS. 42.5% declared they systematically offered patients the generic drug, whereas 55% chose to target specific populations for substitution.</td>
<td>[31]</td>
</tr>
<tr>
<td>Nigeria</td>
<td>Pharmacists</td>
<td>154</td>
<td>Questionnaire</td>
<td>(54.5%) respondents reported that generic medicines were not of equivalent quality to branded ones. Many respondents lacked confidence in the quality of the generics available on the Nigerian market. 92.9% supported generic substitution practices, 68.2% would prefer to recommend generic medicines over branded ones. Hospital pharmacists were more likely than community pharmacists to recommend generic medicines.</td>
<td>[32]</td>
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<tr>
<td>Czech</td>
<td>Pharmacists</td>
<td>615</td>
<td>Questionnaire</td>
<td>61.5% of respondents considered generic drugs as</td>
<td>[33]</td>
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<td>Republic</td>
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<td>attitudes, experiences</td>
<td>bioequivalent and 74.0% respondents as therapeutically equivalent to the respective brand name drugs. 16.1% of pharmacists believed that generic products are of lower quality than branded drugs and 11.2% expected generics to cause more adverse drug reactions. GS was perceived as a positive tool by 77.4%. Only 11.5% respondents showed acquaintance with all the legal rules for GS. Legislation awareness and attitude towards GS was correlated with age. The use of GS in the routine practice depends on the pharmacists' familiarity with the relevant legislation and attitude towards generic drugs and GS.</td>
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<tr>
<td>Germany</td>
<td>Patients</td>
<td>804</td>
<td>Survey</td>
<td>Perceptions</td>
<td>GPs are in an ideal position to inform their patients adequately about the equivalence of brand-name and generic drugs. Patients hold views that inexpensive drugs must be inferior; felt that generic prescribing was &quot;invented&quot; to solve the financial crisis in the German health insurance system at their expense.</td>
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<tr>
<td>Norway</td>
<td>Patients</td>
<td>281</td>
<td>Written questionnaire</td>
<td>Experiences, attitudes</td>
<td>36% of the patients reported negative experiences after medication substituted. Generic drug substitution was not considered an equal alternative to branded drugs by a number of patients for whom additional information and support may be needed. Patients who received information from their physician or the pharmacy about GS were more likely to have switched. 41% of the patients would not switch if they had no personal economic incentives.</td>
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<tr>
<td>Norway</td>
<td>Hypertensive patients</td>
<td>174</td>
<td>Interviews</td>
<td>Challenges of GS in adherence</td>
<td>One in three said generic substitution made keeping track of their medications more demanding. Twenty-nine per cent were anxious when they started to use a generically substituted drug. Eight per cent felt that the effect of the drug had changed, and 15% reported having new or more side-effects. A negative attitude towards generics was significantly associated with low educational attainment, increasing number of drugs, having general concerns about medicine use, and having received insufficient information regarding generic substitution.</td>
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<tr>
<td>Finland</td>
<td>Patients</td>
<td>256</td>
<td>Questionnaire</td>
<td>Preferences</td>
<td>Approximately half of the respondents were strongly price sensitive while the others had other preferences such as brand or an opportunity to buy the medicine at a pharmacy, or to have a physician or a pharmacist as an information source.</td>
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<tr>
<td>USA</td>
<td>Patient</td>
<td>356</td>
<td>Postal survey</td>
<td>Perception of generic AEDs</td>
<td>A significant percentage of patients reported that generic AEDs were responsible for break-through seizures and increased side effects. A significant percentage of patients also reported switching back to a brand-name AED and expressed concern over pharmacies switching to generic AEDs without a patient’s or physician’s consent.</td>
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<tr>
<td>The Netherlands</td>
<td>Patients</td>
<td>106</td>
<td>Interview</td>
<td>Attitudes to substitution, oral atypical antipsychotics</td>
<td>3% stated that they would be unlikely to take a generic antipsychotic if their pharmacist were to substitute it. Providing patients with a short explanation had a significantly positive effect on their intention to take a generic version; however, overall, the patients’ intention to take the generic antipsychotic lay well below a neutral midpoint.</td>
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<tr>
<td>USA</td>
<td>Patients</td>
<td>971</td>
<td>Postal survey</td>
<td>Relationship between beliefs and generic usage</td>
<td>Patients with psychoses/schizophrenia perceive generic versions of their antipsychotics as being significantly different. This perceived difference lowers their intention of continuing to take the medication, thus possibly jeopardizing treatment outcome.</td>
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<tr>
<td>USA</td>
<td>Patients</td>
<td>1054</td>
<td>Postal survey</td>
<td>Perceptions</td>
<td>Generic drug use is most closely associated with communication by providers about generics resulting in comfort with generic substitution.</td>
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<tr>
<td>New Zealand</td>
<td>Consumers</td>
<td>441</td>
<td>Questionnaire</td>
<td>Knowledge, perceptions, attitudes.</td>
<td>Pharmacists were the main source of information regarding generic medicines followed by doctors and media. A higher level of education had a direct relationship with having correct knowledge of generics. Attitude of participants toward the use of generic medicines was determined by their knowledge of generics, whether recommended by a pharmacist and their type of illness. Participants were more prepared to change to a generic for a minor illness (79%) than for a</td>
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<tr>
<td>Australia</td>
<td>Patients: Senior citizens</td>
<td>104</td>
<td>Focus groups</td>
<td>Perceptions</td>
<td>Demonstrated considerable mistrust of generic medicines. Participants highlighted their uncertainty about the extent of pharmaceutical companies’ influence on health professionals, the mistrust of foreign generic manufacturers and scepticism in their equivalence. The substitution of generic medicines and variability in packaging added to the overall concern and reported poor compliance.</td>
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<tr>
<td>South Africa</td>
<td>Consumers</td>
<td>73</td>
<td>Focus groups</td>
<td>Perceptions</td>
<td>Irrespective of socio-economic status, respondents described medicine quality in terms of the effect the medicine produced on felt symptoms. Generic medicines were considered to be poor quality and treated with suspicion. Cost, avoidance of feeling ‘second-class’, receiving individualized care and choice in drug selection were the main determinants influencing procurement behaviour. Participants perceived that they had limited influence on selection of prescription medicines. Generic substitution would be supported if the doctor, rather than the pharmacist, recommended it.</td>
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<tr>
<td>Norway</td>
<td>Patients (Specifically: Pakistani immigrants)</td>
<td>83</td>
<td>Interviews</td>
<td>Challenges following GS</td>
<td>One quarter of the participants were of the opinion that cheaper generic drugs were counterfeit drugs. Two thirds had accepted generic substitution in the pharmacy, whereas the remaining participants had either opposed</td>
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<td>Finland</td>
<td>Public (i.e., consumers)</td>
<td>1844</td>
<td>Postal survey</td>
<td>Opinion</td>
<td>Finnish people consider GS a good reform. They also have confidence in the effect of cheaper medicines. Savings are the main reason for accepting GS. Most of the respondents (88.4%) who had substituted their medicines had not noticed any difference between the previously used and substituted medicines. Substitution was not considered to cause any risk to drug safety. Two main reasons for substituting were a desire to save money and recommendation by pharmacists. Female gender, older age and use of prescription drugs were associated with refusing.</td>
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<tr>
<td>Japan</td>
<td>Patients</td>
<td>1215</td>
<td>Questionnaire</td>
<td>Attitudes to GS</td>
<td>The majority of participants had the correct understanding only on the following two points: generic drugs are less expensive than the brand name drugs (86.0%) and generic drugs contain the same active ingredients as brand name drugs (71.1%). Understanding was poor in other aspects of generic substitution: the</td>
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| Iraq             | Consumers  | 14 | Face to face interviews | Perceptions | Not all the consumers were familiar with the term “generic medicine;” they were familiar with the term “commercial medicine.”
Most of the participants understood that generics cost less compared with their branded counterparts, and their physicians and pharmacists had given them information on generics.
However, knowledge of generic medicines was lacking among consumers in Iraq and their primary reason for using generic medicines was that they were less expensive.
Physicians’ inclinations to prescribe brand-name medicines and lack of knowledge on generic medicines were the main barriers to acceptance of generic medicines. | [51] |
<table>
<thead>
<tr>
<th>Setting/location</th>
<th>Subject(s)</th>
<th>n</th>
<th>Type</th>
<th>Focus</th>
<th>Main findings</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Finland</td>
<td>Public</td>
<td>1844</td>
<td>Postal questionnaire</td>
<td>Opinion on refusal of GS</td>
<td>Main reasons for GS refusal were satisfaction with their current medicine and/or that a decision on a drug product had been made in co-operation with their physician. Most of these individuals indicated that they would be unwilling to accept generic substitution in the future. Economic factors were generally not considered to be an important part of the decision to refuse generic substitution. Respondents trusted and appreciated the opinion of their physicians, reinforcing the role of healthcare professionals in containing appropriate use of GS.</td>
<td>[52]</td>
</tr>
<tr>
<td>USA</td>
<td>Patients</td>
<td>172</td>
<td>Oral questionnaire</td>
<td>Beliefs, perceptions</td>
<td>Awareness of the benefits of generics did not equal preferences for personal use of generics. HC professionals infrequently discussed generics with participants. About a quarter (23.3%) believed that brand-name medications were more effective than generics. 13.4% believed that generics caused more side effects.</td>
<td>[53]</td>
</tr>
<tr>
<td>USA</td>
<td>Patients</td>
<td>30</td>
<td>Focus groups</td>
<td>Perceptions, barriers to use</td>
<td>Barriers to generic medication use included perceptions that generics are less potent than brand-name medications, require higher doses, and, therefore, result in more side effects; generics are not “real” medicine; generics are for minor but not serious illnesses; the medical system cannot be trusted; and poor people are forced to “settle” for generics. Although education about generics could rectify misinformation, overcoming views such as mistrust of the medical system and the sense of having to settle for generics because of poverty may be more challenging.</td>
<td>[54]</td>
</tr>
<tr>
<td>Setting/location</td>
<td>Subject(s)</td>
<td>n</td>
<td>Type</td>
<td>Focus</td>
<td>Main findings</td>
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<tr>
<td>UAE</td>
<td>Renal patients</td>
<td>188</td>
<td>Survey</td>
<td>Views on GS</td>
<td>70% of patients were aware of the availability of generic medicines. 31% felt that generics were not equivalent or only sometimes equivalent to branded medicines. Nearly half (47%) the patients stated they would refuse generic substitution of ciclosporin when it became available if this was just to save the health authority money.</td>
<td>[55]</td>
</tr>
<tr>
<td>Germany</td>
<td>Patients</td>
<td>126</td>
<td>Questionnaire</td>
<td>Perspectives to substitution in context of treatment of epilepsy</td>
<td>32% of the patients who already experienced a switch to generic AEDs complained of problems with the switch. However, patients who had never switched were more concerned about generic substitution than those who had already switched. Patients' beliefs differed between the use of generic drugs in acute medical conditions, such as pain and infections, and the use of generic AEDs in epilepsy.</td>
<td>[57]</td>
</tr>
<tr>
<td>Denmark</td>
<td>Patients</td>
<td>2476</td>
<td>Questionnaire</td>
<td>Attitudes, beliefs and experiences</td>
<td>Patients who had once experienced a generic switch were more likely to accept a future generic switch. Negative views on generic medicines were negatively associated with switching, while beliefs about medicine and confidence in the healthcare system had no influence.</td>
<td>[58]</td>
</tr>
<tr>
<td>USA</td>
<td>Female patients</td>
<td>50</td>
<td>Focus groups</td>
<td>Perceptions</td>
<td>Generally favourable perceptions regarding generic drug discount programs. Study participants believed that generic medicines were generally effective and similar to their brand equivalents; however, there was an association between severity of illness and willingness to utilize generic prescription drugs.</td>
<td>[59]</td>
</tr>
<tr>
<td>Setting/location</td>
<td>Subject(s)</td>
<td>n</td>
<td>Type</td>
<td>Focus</td>
<td>Main findings</td>
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<td>--------------------------------------------</td>
<td>-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
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</tr>
<tr>
<td>Ireland</td>
<td>Patients</td>
<td>42</td>
<td>Interviews</td>
<td>Perceptions</td>
<td>Variable knowledge about generic medicines among patients. Although patients are supportive of their more widespread use, concerns regarding safety, clinical effectiveness, and manufacturing quality of generic medicines were identified.</td>
<td>[60]</td>
</tr>
<tr>
<td>USA</td>
<td>Consumer</td>
<td>183</td>
<td>Survey</td>
<td>Factors influencing purchasing</td>
<td>Single most influential factor was lower cost. Other factors including advertisements, duration of the OTC effectiveness, severity of sickness, preferable form of OTC medication, safety of the OTC, relief of multiple symptoms, and preferred company will persuade consumers to pay more for brand name drugs. 90% reported that they believe OTC generic drugs and brand name drugs to be equally effective and safe and undergo the same FDA approval process, yet only half chose to use generic over brand name OTCs. Discrepancy between reported beliefs and purchasing behaviours.</td>
<td>[62]</td>
</tr>
<tr>
<td>Australia</td>
<td>Patients</td>
<td>47</td>
<td>Postal survey</td>
<td>Attitudes and perceptions to GS with AEDs</td>
<td>Considerable concern was found among patients with epilepsy about generic substitution of antiepileptic drugs - two patients reported that they were advised by their neurologist not to use a generic. More clinical data and research on bioequivalence of generic antiepileptic medicines may help to address these concerns.</td>
<td>[63]</td>
</tr>
<tr>
<td>USA, Europe, Canada, Australia, Brazil and</td>
<td>Consumers</td>
<td>20 studies: 1970-Oct. 2008</td>
<td>Review article</td>
<td>Views Chronological</td>
<td>Mixed reactions, related to development level of country. However, reasonably positive attitude (40-60%) stable across studies. Positive attitudes not necessarily translated into increased use of generic products.</td>
<td>[64]</td>
</tr>
<tr>
<td>Setting/location</td>
<td>Subject(s)</td>
<td>n</td>
<td>Type</td>
<td>Focus</td>
<td>Main findings</td>
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<tr>
<td>Malaysia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Confidence and knowledge have improved, particularly in developed countries – probably due to mass educational efforts, financial incentives and greater communication amongst patients. Branded preferred until price differential is great enough – financial incentives are the greatest predictor of generic usage. Role for pharmacist in increasing generic usage. Less inclination towards usage and acceptance of generics by patients with serious illnesses. Lower income + less education = more negative attitudes. Safety and efficacy issues = major barriers to uptake of generics.</td>
<td></td>
</tr>
</tbody>
</table>

| Ref |
Figure 1 – Flow charts of selection methodology by stakeholder group (PubMed)

**Physician/GP** perception, opinion, attitude or view, n = 276

- Following review of titles and abstracts to exclude those outside scope, n = 19
- Exclude any not in English, n = 6
- Addition of review article (n = 1), Irish article outside scope (n = 1) and non PubMed referenced texts (n = 1), n = 3
- Final number of papers reviewed, n = 16

**Pharmacist** perception, opinion, attitude or view, n = 90

- Following review of titles and abstracts to exclude those outside scope, n = 10
- Exclude any not in English or where full text could not be sourced, n = 0
- Additions, n = 0
- Final number of papers reviewed, n = 10

**Patient/consumer** perception, opinion, attitude or view, n = 602

- Following review of titles and abstracts to exclude those outside scope, n = 34
- Exclude any not in English, n = 5
- Addition of review article (n = 1), n = 1
- Final number of papers reviewed, n = 30
<table>
<thead>
<tr>
<th>Theme</th>
<th>Sub Themes</th>
<th>Examples of Contributing Papers</th>
</tr>
</thead>
</table>
| Pharmacists’ concerns regarding patient understanding of generic medicines and substitution, patient safety and compliance with treatments | a. Patient confusion  
b. Concerns regarding interchangeability.  
c. Problems with patient compliance. | a. [25-27, 30, 33]  
b. [25, 27, 28, 30, 32, 33]  
c. [25, 27, 30, 32] |
| Pharmacists’ understanding of generic medicines and substitution, and pharmacists’ confidence in quality, efficacy and safety of generic medicines | a. Level of confidence in knowledge.  
b. Hospital based pharmacists vs. community pharmacists.  
c. Need to contact prescriber.  
d. Belief that the patient prefers physician opinion.  
e. Requirement for adverse event reporting. | a. [18, 27, 29, 30]  
b. [32]  
c. [25]  
d. [26, 27]  
e. [28, 30] |
| Practical aspects of pharmacists’ practice as affected by generic medicines and substitution | a. Financial incentives by pharmaceutical industry.  
b. Increased pharmacist workload.  
c. Adverse effect on stocking levels.  
d. Influence of industry representatives. | a. [18, 26, 30-32]  
b. [25, 27, 28, 30, 32]  
c. [25, 27, 33]  
d. [18, 26] |
| Pharmacists’ suggestions to improve generic medicines use and education of stakeholders | a. General education needed.  
b. Patients should have a role in medication decision.  
c. Need for change in prescribing patterns. | a. [18, 26-31, 33]  
b. [25, 27]  
c. [26, 27, 31] |
Table 3: Unifying Themes and Contributing Sub-Themes from Patient Papers

<table>
<thead>
<tr>
<th>Theme</th>
<th>Sub Themes</th>
<th>Examples of Contributing Papers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients’ lack of confidence in generic medicines,</td>
<td>a. Scepticism</td>
<td>a. [35, 39, 41, 42, 44-48, 52-55, 57, 58, 63]</td>
</tr>
<tr>
<td></td>
<td>b. Provision of poor or poorly understood information</td>
<td>b. [35, 39, 46, 53-55, 59]</td>
</tr>
<tr>
<td></td>
<td>c. Concerns regarding packaging and/or appearance of generic medicines</td>
<td>c. [35, 39, 41, 42, 45, 46, 51]</td>
</tr>
<tr>
<td>Patients actual experiences in using generic medicines,</td>
<td>a. Poor experience</td>
<td>a. [35, 36, 39, 41, 48, 52, 57]</td>
</tr>
<tr>
<td></td>
<td>b. Not exclusively negative</td>
<td>b. [35, 36, 41, 42, 49, 58]</td>
</tr>
<tr>
<td></td>
<td>c. Difficulties associated with treatment adherence or compliance</td>
<td>c. [39, 42, 46, 48, 51, 57]</td>
</tr>
<tr>
<td>Factors influencing patient acceptance of generic medicines</td>
<td>a. Patient involvement in decision-making</td>
<td>a. [41, 42, 52, 59, 63]</td>
</tr>
<tr>
<td></td>
<td>b. Advanced age incompatible with generic use</td>
<td>b. [36, 49]</td>
</tr>
<tr>
<td></td>
<td>c. Income/Education level</td>
<td>c. [44, 45, 53]</td>
</tr>
<tr>
<td></td>
<td>d. Severity of illness/Drug type</td>
<td>d. [39, 44, 45, 53, 54, 57, 59, 62]</td>
</tr>
<tr>
<td></td>
<td>e. Nocebo</td>
<td>e. [35, 60]</td>
</tr>
<tr>
<td>Provision of information and education regarding generic medicines</td>
<td>a. Education and supports</td>
<td>a. [36, 39, 42, 44, 48, 50, 51, 55, 59, 62]</td>
</tr>
<tr>
<td></td>
<td>b. Source of information, including physician vs. pharmacist</td>
<td>b. [46, 47, 54]</td>
</tr>
</tbody>
</table>
Chapter 3

Perceptions of Generic Medicines Amongst General Practitioners, Community Pharmacists and Patients in Ireland.
Chapter 3

ABSTRACT

Background

To benefit from cost-savings associated with generic medicine use, in June 2013 Ireland introduced generic substitution and reference pricing. Attitudes and behaviours of patients and healthcare professionals may influence successful implementation of such changes. Prior to this PhD-related research, perceptions of patients and pharmacists in Ireland towards generic medicines had not been published previously and only one study of physician perceptions in Ireland had been published, dating from 1997.

Objectives

The aim of this chapter therefore is to evaluate the attitudes of healthcare professionals and patients towards generic medicines and to explore the role of other potentially important contextual factors, relating to behaviours towards generic medicines, using qualitative methodology. This study will also compare current perceptions amongst GPs and community pharmacists in Ireland with the only existing published information, to determine if any changes have occurred over time.

Methods

Detailed, one-to-one semi-structured interviews were performed with representative cohorts of 34 GPs, 44 community pharmacists and 42 patients, in Ireland. These interviews additionally included a quantitative segment for evaluation of attitudes, which used a five-point Likert scale for responses. Interviews were transcribed and analysed using a directed content analysis approach based on the Theory of Planned Behaviour (TPB) to investigate specific attitudes, subjective norms and perceived behavioural control constructs related to usage of generic medicines.

Findings
Quantitative analysis revealed that attitudes to generic medicines were very positive in the professional groups, with GPs showing marginally less confidence in generics than pharmacists. The patient cohort demonstrated the greatest level of negative attitudes towards generics. Qualitative analysis uncovered several inter-related constructs and themes (TPB and non-TPB) that were influential on perceptions and behaviour toward generics. Social, and particularly moral, norms were important in the professional groups, but moral norms were not seen to be important in the patient group. Cost appeared to be the singular barrier for patients, but many controls or barriers to usage of generics were noted for the professional groups. These included, but were not limited to, familiarity with trade names, patient preference, clinical constraints, lack of government incentive for generic prescribing and change management. Several non-TPB influencers were also identified in terms of macro-level determinants and the roles and relationships between the cohorts.

Conclusion

Attitudes to generic medicines in Ireland have become substantially more positive since 1997. This study elucidates further substantial detail around many additional areas that determine behaviours towards generic medicines. These serve to supplement knowledge about behaviours – as attitudes are not the single determinant of human behaviour. Theoretical approaches that take other factors into account, such as the TPB, help us to understand decision-making and resultant behaviours. This study, therefore, provides information on areas where future interventions (that may be planned) targeting improvement of generic medicine usage in Ireland, could be focused to provide enhanced results in terms of changes in behaviour towards acceptance and usage of generic medicines.
INTRODUCTION

Attitudes of healthcare professionals towards generic medicines have been studied internationally [1-3], with many country-specific studies reported including: Australia [4]; Italy [5]; South Africa [6]; Malaysia [7, 8]; Saudi Arabia [9]; Jamaica [10]; France [11, 12]; New Zealand [13]; Portugal [14]; Sweden [15] and USA [16]. These studies have found that physicians express concerns about the overall quality and reliability of generic drugs as well as perceptions that the safety and efficacy of generic medicines are lesser than that of proprietary formulations. Pharmacists tend to hold mainly positive views of generics relating to their safety and equivalence but have expressed concerns about the quality of these medicines.

However, prior to this PhD thesis, only one peer-reviewed study had been published reporting the attitudes of healthcare professionals in Ireland towards generic medicines. That study, published in 1997, determined general practitioner (GP) opinions, and showed that the majority of GPs (75%) were concerned about the reliability and quality of generic medicines [17]. Additionally, a report, prepared for the Irish Minister for Health in 1997, stated that half of the pharmacists surveyed believed that some generic medicines were unreliable [18]. Therefore, one of the aims of this study is to investigate if attitudes, as represented in the above two documents, have changed in the interim period.

In contrast to the relatively limited studies of professionals as described above, patient opinions towards generics have been considerably more widely studied. Published reports have originated in Norway (patients attitudes to generic substitution) [19], Finland (preferences of patients for generic and branded OTC (over-the-counter) pain medicines) [20], Portugal (patient perceptions of underuse of generics and their attitudes towards generic substitution) [14], South Africa (consumer perceptions of generic drug quality compared with actual drug quality) [6, 21], New Zealand (patients’
perceptions, knowledge and attitudes regarding generic medicines and investigation of patients' attitudes towards generic substitution of oral antipsychotics) [22, 23], Iraq (consumers’ knowledge relating to generic medicines) [24], the United States (patient knowledge of, and attitudes relating to, formulation switching of antiepileptic drugs) [3], and Ireland (patient perceptions of generic medicines) [25], amongst others.

Reported attitudes amongst patients tend to be more negative than those reported for professional groups and are mainly related to patients’ beliefs that generics are not as effective as proprietary medicines; that cheaper equals inferior, thus: a belief that generics are of lower quality and are considered “second class” relative to proprietary brand medications.

Attitudes, however, are not the single determining factor of human behaviour; thus, other determinants may be important influencers of behaviours related to acceptance and usage of generic medicines. Factors such as social influences (normative social factors prevailing for any given individual) and any perceived barriers or controls to behaviours (which may be either internal to the individual, such as ability or self-efficacy, or external to the person, such as culture, policy or legislation) also impact on decision-making and thus behaviour. In other healthcare contexts (e.g. searching for healthcare information; evaluation of therapy support programmes; assessment of intention to integrate research evidence into clinical decision making; and assessment of physicians’ intentions and beliefs towards prescribing, amongst many others), theoretical approaches to understanding these processes and behaviours have been applied [26-31]. One of the most consistently applied theoretical frameworks is the Theory of Planned Behaviour (TPB) [32].
Ajzen’s Theory of Planned Behaviour (TPB) [32] is an individual level behaviour theory that helps clarify the psychological and social variables involved in human behavioural decision-making. The TPB states that intention, one of the immediate determinants of behaviour, depends on three constructs: attitudes towards the behaviour, subjective norms and perceived behavioural control [32]. Furthermore, addition of variables to the TPB can increase its capacity to predict intention, for example, moral norms have been shown to be a determinant of behavioural intention [33]. Moral norms refer to a person’s feeling of moral obligation towards performing a given behaviour, and the correspondence between said behaviour and his or her principles. TPB has been used widely to understand various behaviours in the field of healthcare research, for example: in the areas of evaluation of therapy support programmes [26]; searching for healthcare information [27]; assessment of intention to integrate research evidence into clinical decision making [28]; understanding of sugary beverage consumption in adults [29]; in assessment of physicians’ intentions regarding prescribing of antibiotics specifically [30]; and in the eliciting of GPs’ beliefs towards prescribing [31], amongst others. Moreover, a systematic review of studies based on social cognitive theories, which investigated healthcare professionals’ intentions and behaviours in clinical settings, determined that the TPB was an appropriate tool to predict healthcare professionals’ behaviours [34].

The aim of this chapter therefore is to evaluate the attitudes of healthcare professionals and patients towards generic medicines and to explore the role of other contextual factors that may be important for perceptions and behaviour, using qualitative methodology. This study will also compare current perceptions amongst GPs and community pharmacists in Ireland to the only existing published information on this topic, to determine if any changes have taken place over the intervening time period.
Given that the attitudes toward generic usage are well established, these will be evaluated quantitatively. Moreover, to understand the other important influencers of perceptions and behaviours a directed content analysis will be employed as our qualitative analytic strategy. Further, given that we are being guided by the TPB, a theory driven approach will be used, i.e. a directed content analysis [35]. Concepts from the TPB will facilitate analysis and structuring of the data from interviews undertaken with these cohorts (that is: general practitioners, community pharmacists and patients). It is important to note that a key strength of a directed approach is that not only can existing theory be supported but it can also be extended. Therefore, the researchers should remain open to considering and generating new concepts that may be important in this context [35]. This is consistent with other research in the healthcare area, which has used the TPB, but strengthened the utility of the model by recognising that additional variables have an impact on behaviour, for example (but not exclusively): risk avoidance [36], stigma [37], or understanding or knowledge of the topic [38].
METHODOLOGY

Design

A mixed methods study to determine the attitudes, perceptions and other contextual factors (such as subjective norms and perceived behavioural controls) that may be important for behaviour towards generic medicines, in three cohorts representing principal stakeholder groups engaging with medicines provision and use, in Ireland; namely: general practitioners (GPs) (as representatives of prescribing physicians); community pharmacists (as representatives of medicines dispensers); and patients (as consumers of medicines). Data analysis of the different data sources followed the principles of content analysis for quantitative assessment of attitudes towards generic medicines - performed using attitudes already established in the literature as a basis for examination. Further assessment, using qualitative methods, explored other determinants of behaviours towards generics.

Quantitative component

Attitudes

Attitudes measured were derived from the existing literature on the topic and included questions relating to quality, efficacy, safety and personal preference for use of generics. See Table 1 for questions.

Statements were read out (one-by-one) to participants who provided a response indicating agreement or disagreement with the statement, selected from pre-defined answers. A five-point Likert scale was used for responses, with a single answer allowed for each statement, selected from: Strongly Agree, Agree, Neutral, Disagree and Strongly Disagree (example statement, in terms of efficacy: generic medicines work as effectively as originator medicines). The same questions, without variation, were posed
to each cohort. Where participants provided further narrative during answering of these quantitative questions, this was included in qualitative assessment.

Cronbach’s alpha was calculated to measure the internal consistency of responses from participants to all items, after reverse coding the negatively worded statements. A chi-square test was used to measure the association between type of respondent (GP, pharmacist and patient) and level of agreement with the statements combined into three categories (Disagree, Neutral and Agree). A 5% level of significance was used for all statistical tests and no adjustment was made for multiple testing. The statistical software package IBM SPSS Statistics for Windows Version 20.0 was used for analysis.

**Qualitative component**

**Setting, Sampling, Recruitment and Interviews**

Convenience samples of members of the three cohorts were recruited, and interviews completed and analysed, as described below:

**General Practitioners**

Invitation letters (which included details of the study) were sent to a total of 65 GPs located in the South of Ireland (these comprised the cohort of GP practices affiliated with the Graduate Entry Medical School in the University of Limerick at the time of the study). Acceptance emails or telephone calls were received from a number of GPs and interview times were arranged. The invitation letter was followed up with a telephone call, 1-2 weeks later, for those GPs who had not already accepted, and interviews were arranged with those who consented to participate. Purposeful sampling of participants, based on geographical location, was used at this stage in order to ensure geographical
spread of participants – taking into account both urban and rural locations (18 urban, 16 rural).

One-to-one interviews were carried out with consenting participants between June and August 2012 (all interviews except one (which was face-to-face) were completed using the same method, that is, via telephone). Interview lengths were as follows: minimum – 9 minutes 25 seconds; maximum 23 minutes 48 seconds; mean – 15 minutes 39 seconds. Interviews, which were recorded (with each interviewee's permission), were semi-structured and based on the instrument developed as described below. Participants were free to volunteer additional commentary on each question and were also offered the opportunity to express freely any additional opinions or views at the end of the interview session, the aim being to potentially tap into TPB elements and additional factors which had not been specifically probed in the interview.

Participating GPs (over half (34) of the 65 GPs affiliated with the Graduate Entry Medical School took part in this study) were located in the South, South-East and Mid-West of Ireland in counties Limerick, Tipperary, Kerry, Kilkenny, Cork and Waterford.

Community Pharmacists

Pharmacists were approached in person, while in the pharmacy, and invited to participate in the study. A verbal explanation of the study was provided, and an invitation letter was offered. One-to-one interviews were carried out with consenting pharmacists between June and October 2012: 34 face-to-face and 10 via telephone. Interview lengths were as follows: minimum – 10 minutes 44 seconds; maximum 36 minutes 15 seconds; mean – 19 minutes 29 seconds. Interviews, which were recorded (with the interviewee’s consent), were semi-structured and based on the described study instrument. Additional supporting assessment of opinions was completed using of a series of structured questions to which participants could select from pre-defined
answers (in a manner identical to that described for the GP cohort). Participants were free to volunteer additional commentary on each question or add what they felt was not captured in the interview questions. Participating pharmacists were located in counties Limerick, Tipperary, Kilkenny, Cork and Waterford.

Patients

Patients were recruited from three GP practices affiliated with the University of Limerick’s Graduate Entry Medical School and from community pharmacies, the collective group of which were based in counties Limerick, Tipperary, Cork, Kerry, Kilkenny and Waterford. Patients, from both urban and rural locations (throughout the South, South-East and Mid-West of Ireland and therefore broadly reflective of Ireland’s socio-demographic profile) were approached, in person, and invited to participate in the study. All patients present in the GP surgery waiting room/community pharmacy were invited, orally, to participate. If willingness to participate was expressed, the study was explained to them verbally, a written explanation (patient participation leaflet) was provided and they were then entered into the study. As per the granted ethical approval, agreement to participate in the study was taken as patient consent (no signed consent forms were required). Patients waiting to see their GP were interviewed on the day (in a private consultation room). Those recruited from community pharmacies were interviewed either face-to-face or via telephone (as arranged when consent to participate was given). In total, 35 interviews took place face-to-face, and 7 were via telephone. Interview lengths were as follows: minimum – 7 minutes 10 seconds; maximum 14 minutes 38 seconds; mean – 10 minutes 41 seconds. All interviews were performed with consenting patients between November 2012 and April 2013. As with the other interviews, patients were offered the opportunity to express freely any additional opinions or views at the end of the interview session.
The rationale for sampling from two differing locations (GP surgeries and pharmacies) was to obtain the fullest range of opinions possible. While those recruited from the GP surgeries were likely to be feeling unwell, some of those recruited from the pharmacies may have been there to collect prescriptions for other people, or to purchase over-the-counter (OTC) medications for minor illnesses.

**Anonymisation**

Each participant was assigned an anonymised identifying code as follows: GPs: GP1-GP34, Pharmacists: Ph1-Ph44, and Patients: Pa1-Pa42. To protect the identities of participants, no names or other identifying characteristics were recorded on the interview notes. The candidate performed the interviews in all cases. The interviewer had formal training on design of questionnaires and completion of interviews and is also a professional lead auditor of quality management systems, and a qualified trainer and business coach.

**Development and refining of study instruments**

Questions forming the basis of semi-structured interviews were prepared, discussed and agreed with the project supervisors. Three study instruments were produced, one for each cohort. The questions focused on exploring the prescribing habits, dispensing activities, and experiences and beliefs around the use of generics, for physicians, pharmacists and patients respectively. Further, probes were used throughout all interviews when interesting comments were made to see clarification and more understanding. As mentioned previously, all participants were given the opportunity to any additional information or commentary that was not covered by the interview.
Iterative development of the study instruments

To ensure understanding by participants, the agreed upon interview questions were subjected to cognitive testing. The intent of the interviews was to elucidate general opinion, understanding & perceptions of generic medicines; behaviours towards generic medicines (e.g., prescribing behaviours in the case of GPs and dispensing behaviours in the case of community pharmacists); opinions as to barriers to use of generic medicines in Ireland; beliefs held as to the quality and efficacy of generics and how these products compare to proprietary (that is, brand-name) medicines. Therefore, the aim of the cognitive testing was to ensure that the questions were understood as intended.

Cognitive testing was performed with three individuals in each cohort group who were asked the questions, allowed to provide responses and after responding were asked what their understanding of the questions was. Several iterations of amendments were made to questions based on responses from all nine test participants and collaborative discussion with research supervisors. The responses of these participants to the interview questions were not included among those finally analysed for this study. The interviews used in the study began after cognitive testing had been completed and the interview questions had been amended. These finalised structures were not further altered as interviewing progressed.

Analytic Strategy

For clarity: the analysis described in this chapter was completed retrospectively, using data included in chapters 4 to 7.

Interviews were transcribed, verbatim, imported into NVivo (version 9) and analysed using a directed content analysis approach [35, 39]. Directed content analysis is used where prior research exists about a phenomenon under study. Qualitative content
analysis is a method used to analyse text data; this focuses on the characteristics of language as communication with attention to the content or contextual meaning of the text, thus providing a methodology for classifying large amounts of text into an efficient number of categories that represent similar meanings (codes), representative of either explicit or inferred communication. The goal of content analysis is to provide knowledge and understanding of the phenomenon under study [39].

In relation to these studies, a body of data exists in the literature regarding perceptions of stakeholders towards generic medicines; however, there is a knowledge gap specifically related to the Irish context. The existing information, along with the researcher's own experience and knowledge, were used to design the study. The content analysis, using a directed approach, was guided by a structured approach using the existing information to identify key concepts as initial coding categories. Any information from the interviews that could not be categorised within the initial coding scheme was given a new code.

To organize the data, the Theory of Planned Behaviour (TPB) [32] was used as the core coding framework. This social cognition model has been widely used to predict individual behaviours, and has been one of the theories used most often when exploring determinants of behaviour. The theory states that an individual's intention to perform a behaviour is the proximal predictor of behaviour. In turn intention is predicted by attitude (the degree to which a person has a favourable or unfavourable evaluation or appraisal of the behaviour in question), subjective or social norm (the perceived social pressure to perform or not to perform the behaviour) and perceived behavioural control (the perceived ease or difficulty of, or barriers in place affecting, performing of the behaviour).
Two researchers (SD, SG) reviewed data and developed the core coding plan, based on
the TPB, to analyse data according to: attitudes relating to generic medicines,
subjective (that is: social or moral) norms relating to use of generic medications and
perceived or actual behavioural controls related to current and previous usage of
generics, bearing in mind that such controls may be internal to the individual in
question, or external to the person.
Initially, transcripts were read in-depth, line-by-line, to identify items that were
consistent with subjective norms and perceived behavioural controls (PBCs).
Furthermore, while coding was primarily according to the principles of the TPB, there
is a recognition that this theory can be limited in its information gathering ability.
Therefore, in order to be receptive to new ideas and to other important information that
may surface during analysis, an openness of mind was maintained during the coding
process to inductively identify any new ideas (codes) - possibly not consistent with the
TPB. Therefore, themes which were not consistent with the TPB, but which may also be
factors influencing behaviours towards generic medicines were also identified and
initially coded into an “other” category.
The transcripts were then re-read to further classify the TPB items into more
descriptive codes. For subjective norms, items were further classified as being “social
norms” or “moral norms”. PBCs were further classified into those that were internal to
the individual, and those that were external and potentially outside of the individual’s
control (e.g. legislative requirements). Items coded to the “other” category were re-
visited and structured to cluster these items into meaningful units. Examples of codes
used in this area were: legislative and policy influences; macro level influences;
relationships between the cohorts; education provision and cross-cultural comparisons.
The transcripts were revisited again to identify any further themes in the non-TPB
items and to cluster the resultant codes into common groups. See Figure 1 for further
detail on the development of the non-TPB coding structure.

Further re-reading of the transcripts uncovered some elements that were consistent
with the attitudes aspect of the TPB and overlapped with our quantitative component.
While the initial coding was not looking for items consistent with this construct, as
attitudes had been assessed using the quantitative data, this further re-read of the
transcripts led to qualitative data being coded to “attitudes”, thereby further
supplementing and providing consistency with the TPB.

After the first sample of interviews had been jointly analysed (approximately 5
interviews), the coding theme was discussed with the project supervisor (SG) in order to
reach consensus on the emerging thematic framework. Once the coding was agreed, the
same approach was used from there forward. SD analysed all remaining interview
transcriptions according to the agreed coding plan. However, there were occasions when
further supervisory advice was needed to clarify categorical and coding schemes for the
‘other’ category. This also applied at the final theoretical development stage.

**Field notes & memoing**

During interviewing and analysis, field notes and memoing were used by the researcher
to record observations, theorizing of ideas about codes emerging from the data, and
their relationships. Notes taken during interviewing were consulted during the coding
process. Furthermore, as coding was on-going, inter-relationships, divergences or other
researcher observations were noted using the memoing function in Nvivo.

**Respondent validation**

Member checking/respondent validation was not used due to the practical constraints
with regard to making renewed contact with the participants after the interview event
(particularly in relation to contacting patients), as well as the potential breach of the granted ethical approval (i.e., in relation to identifying participants and not maintaining anonymised notes).

**Ethical Approval**

Approval of the design and conducting of this study was granted by the Research Ethics Committee of the Irish College of General Practitioners (ICGP).
RESULTS

A total of 120 interviews were performed (34 GPs, 44 community pharmacists & 42 patients).

Quantitative

Attitudes

Attitudes of participants were primarily determined using the structured, closed questions and a psychometric scale. These established participant attitudes relating to the comparative quality, efficacy and safety of generic medicines, in addition to personal preferences regarding use of generic medicines, relative to their originator counterparts.

Chronbach’s alpha

The internal consistency of responses from participants to all items was excellent (Cronbach’s alpha=0.90).

Attitudes towards quality of generic medicines were very positive across all three cohorts, with the greatest level of positive sentiment being seen in the pharmacist group, where only one participant (of 44) exhibited a negative attitude. The greatest level of negativity was seen in the patient group, where 9 participants (of 38 who gave responses, 24%) stated a belief that generics were of poorer quality relative to originator medicines. Within the GP cohort, only 3 of the 34 participants (9%) stated a negative belief with respect to comparative quality of generic medications.

In terms of efficacy of generic medicines, again the greatest level of positive attitude was exhibited in the community pharmacist cohort, with only 2 participants (5%) stating a negative belief regarding comparative effectiveness. The patient cohort
again demonstrated the highest degree of negative attitude, with almost a quarter of participants demonstrating a belief that generic medicines are less effective than originators. The GP group expressed quite positive attitudes towards effectiveness, with only 4 participants (12%) taking a negative position.

With regard to safety of generic medicines, 100% of community pharmacists agreed that they were as safe as originators, with some reticence being demonstrated in the GP and patient cohorts. However, over 80% of both the GP and patient groups had positive attitudes in this regard.

Only one pharmacist and one GP expressed an attitude that generic medicines were less expensive due to being of inferior quality, however 11/38 patients (29%) held this view (with a further five (13%) taking a neutral standpoint).

In terms of personal preference, pharmacists again demonstrated the most positive attitudes with a majority (41/44, 93%) stating that they would be happy to take a generic medicine themselves and that they would not wish to take the originator medication in preference to the generic (39/44, 89%). A majority of GPs also held the view that they would be happy to take a generic (32/34, 94%). However, relatively more GPs than pharmacists would choose the originator over a generic (5/34 (15%) with a further 6 (18%) expressing a neutral opinion). The majority of the patient cohort was also of the view that they would be happy to take a generic medicine (34/38, 89%). However, in relation to preference, the most substantial level of negative attitude was observed in this cohort, with 26/38 participants (68%) stating that they would not wish to take the originator medication in preference to the generic.

Attitude changes since 1997

The only previously published study which investigated GP attitudes towards generic medicines in Ireland [17] found that 75% of prescribers were concerned about the
reliability and quality of generic drugs. That attitude, expressed in 1997, contrasts greatly with the GP opinions expressed in this study, where over 91% of GPs interviewed stated their confidence that generics are of comparable quality to originator medications. This clearly indicates that a considerable shift in the views of general practitioners has occurred in favour of generic medicines. While no previous peer-reviewed publications exist which give a historical perspective on the perceptions of Irish pharmacists towards generics, a report from 1997 (for the then Irish Minister for Health, on a previous attempt by the Irish Government to improve use of generics [18]) stated that about half of pharmacists believed that some generic drugs were unreliable. This, again, is in complete contrast to the findings of this study and indicates a significant change in the opinions of pharmacists in the intervening time period.

**Qualitative**

During the coding process, certain nuances were seen to emerge from the interview data. These showed that PBCs were less evident in the patient group relative to the professional groups and that patient behaviours appeared more likely to be shaped by their attitudes towards generics and the social norms that they are exposed to. Within the professional groups more negative attitudes were evident in the GP group, relative to the pharmacist group. Social norms, particularly moral norms, were again more evident as an influencer within the GP group with fewer items being coded in this area within the pharmacist cohort. Moral norms, however, were evident as an influencer of behaviour in both professional groups, in sharp contrast to the lack of evidence for this as an important influencer in the patient cohort.
Below we discuss elements of the TPB across the three cohorts. Additionally, the previous quantitative assessment of attitudes towards generic medicines was also confirmed through qualitative conversations.

**General Practitioners**

Within the GP group the majority of comments were positive, for example, one participant said how he was taking a generic statin and felt that he was “just as well off on it” relative to the originator (GP12). However, some negative opinions were also evident, with GPs having concerns about equivalency and the patient experience:

*I have seen relatively frequently that people have taken a generic and have had some problem with it – either an actual or perceived side effect (GP17).*

**Community pharmacists**

The pharmacist group held overwhelmingly positive attitudes towards generic medicines, and generic substitution, expressing beliefs that Narrow Therapeutic Index (NTI) and other similar medicines aside from generic medications were just as safe and effective as their proprietary counterparts. Only two of the participants stated substantially negative views and, interestingly, these were the only two community pharmacists interviewed who were non-Irish. One of these stated that they “didn’t do generics”, indicating that he preferred to stock branded medications and other one expressed a view that generics were less expensive due to being of lower quality. Negative comments were made in relation to quality of some generics, with crumbling tablets and difficulty in getting tablets out of blister packs cited as examples, but many who stated these views also said that this was more historical than current, and that the vast majority of generics that they dealt with did not show any quality problems.
Patients

Patients expressed the greatest level of negative attitude towards generic medicines, with perceived lack of efficacy being a substantial issue and several stating the belief that lower cost equated to poorer quality. One patient (Pa13) expressed a view that generics were a “step down” from the “top tier” medicines that were the proprietary brands.

*Well I'd imagine that the branded medicine would be more tested and that you'd probably get a better result from it, and maybe less side effects than you'd have with the unbranded* (Pa8).

Patients expressed a belief that use of lower quality ingredients was a reason why generic medicines were less expensive and, thus, not as effective. However, many patients stated positive views and cited positive previous experiences with generics. Several made reference to the belief that with the proprietary medication “you were just paying for the name” and possibly superior packaging, but that the medicine itself was the same.

Subjective (social and moral) norms

General Practitioners

GPs frequently mentioned the influence of pharmaceutical company sales representatives on their prescribing practices, and linked this with a tendency to prescribe by trade name rather by the generic name of the medicine. This links with the TPB in that it shows how the influence of others can be a determinant of behaviour. However, many expressed positive sentiments in relation to the practice of prescribing by the generic name of the medicine – with the exception of medicines where bioequivalence has not been proven, or in the case of NTI drugs.
Mention of the cost benefits was a recurring theme – and introduces the construct of “moral norms” to this topic, indicating that it is not just societal influence that can be a determinant of behaviour, but also that the concept of “moral dilemma” is also a factor. Advantages both to the health service (in relation to public patients where the State is the payer) and to the private individual were referred to. Furthermore, the cost savings generated by use of generic medicines were believed to have the potential to be put to better use elsewhere in the health system. For example, one GP stated that s/he could not justify overpaying when there was a less expensive alternative available and that the “money saved could be better spent in other areas of the health service” (GP28). This was sometimes linked with provision of jobs by generics manufacturers located in Ireland, indicating a belief in a positive relationship between usage of generics manufactured in Ireland and a benefit to the Irish economy. Interestingly, some of the older GPs made reference to “keeping up with” new medical students or younger physicians coming into their practices; the implication being that the younger generation of physicians tend to prescribe by the generic name more than the older generation did, and that older physicians are adjusting their behaviours to be in-keeping with newer practices, again demonstrating consistency with the subjective norms construct in the TPB:

Being affiliated with the University Medical School, that’s made me change, it’s upped my generic prescribing because the medical students are coming into the practice and they’re only talking generics and I’m trying to speak their language, so I’m prescribing less branded and more generic (GP3)

Community pharmacists

Pharmacists frequently referred to the high cost of medications and the economic climate in Ireland. Similar to sentiments expressed by GPs, the cost to privately-paying
patients, as well as to the public purse, were moral norm references made by a majority of participating pharmacists. In fact, moral norms were more often cited than social norms, indicating that this factor is a greater influencer of behaviour amongst community pharmacists. Also mentioned quite frequently was the fact that the generic version is often not cheaper than the branded medicine in Ireland, and that often (when the generic is less expensive) the actual price difference is very small and provides little incentive to the patient. Again, these moral and societal norms are consistent with the behavioural influencers that comprise part of the TPB.

Pharmacists further made reference to the situation with branded generics in Ireland, with all who mentioned it expressing a negative opinion. Views related to the counter-intuitive nature of branding a generic preparation and to the fact that there were practical implications within the pharmacy in terms of having to stock different “brands” of one generic medication.

_The whole thing with putting a brand on a generic is ridiculous. This whole thing in Ireland around branding generics, there's absolutely no need for it whatsoever_ (Ph13)

Several pharmacists indicated the influence of the pharmaceutical industry in Ireland – both in terms of the influence on prescribers and also the sway that the pharmaceutical industry might have on the government, given the high numbers employed in this industry. One pharmacist told a story of how a patient had complained about having received a generic statin: the story told of how the patient had been happy to accept the generic, however her son worked for Pfizer and when he saw the generic version of the medication he had had “a hissy fit” and insisted she return the generic and exchange it for Lipitor (the proprietary brand).
Patients

There were many references made by this cohort relating to friends and family members who had had negative experiences with generics.

My mother was given a generic and she had way more side effects on it, she didn’t like it at all. So there was obviously something in it that was causing that. When she was stitched back to the original medication she was fine again. (Pa34)

The most common anecdotes referred to a generic medication not being as effective as the branded medication, to more or different side effects being experienced when taking a generic, or to the changing appearance of generics and the confusion that this causes – particularly for elderly family members.

A view was also expressed that there is a substantial societal belief in the superiority of branded medications and that a higher value is often placed on these. There was also an expression that public patients (that is, those holding GMS cards) feel that they are being given “the cheap tablets” because of their status as public patients, further reinforcing the idea of generic medicines being inferior to proprietary medicines.

The above expressions of mistrust or lack of confidence in generics appear to lead to the patient group’s expression of preference for branded medication as seen by the other stakeholder groups. Interestingly, however, many patients made reference to the influence of their GP, stating that – despite negative attitudes and social norms – they would be willing to take a generic medicine if it was prescribed for them by their GP.

Pa40: Well if [my GP] prescribed it for me, yeah, I’d take it all right.

Q: Even though you said previously that you don’t think generics are as good as brand name medicines. Would you be willing to take a generic if your GP prescribed one for you?

Pa40: Yeah I would, I’d trust that she’d know if it was good or not.
**Perceived Behavioural Controls (PBCs)**

**General Practitioners**

Barriers to prescription and use of generic medications were expressed by GPs in terms of controls at the individual level (that is, internal to the person) and those perceived as being external to the person (e.g. legislation). Many GPs stated that familiarity with trade names or “laziness” was a contributory factor to their continuing to prescribe the proprietary brand after a generic alternative has become available.

From the perspective of barriers to generic prescribing that are perceived as being external to the individual, shortcomings with prescribing software was often cited (the main reason given was that the software defaults to the trade name of a drug).

Substantial reference was also made to the influence that patients have on the prescribing process, with many GPs stating that they will acquiesce to a patient’s stated preference to receive a branded medication where an equivalent generic is available. To further this point, many physicians also referred to patient compliance as an issue with use of generics. Several references to confusion being caused by changing appearance (shape, size, colour etc.) of generic medicines, which can result in clinical issues, particularly with elderly patients, were made with GPs being of the view that they would be “more inclined to go with the brand name purely so that the patient gets the same thing each time” (GP11). It is important to note that while patients’ beliefs are a perceived barrier to generic prescribing, there is a negotiation between two parties (GP and patient) which influences behaviour in this scenario. Thus, this is not necessarily consistent with the TPB as the outcome of the situation may rely on other factors, such as the persuasion skills of either party. Furthermore, this example demonstrates where there can be overlap within the TPB as, while patient preference is a perceived barrier to GP behaviour in this case, as discussed, the motivation to help the patient could also
be stated as being an influencer of GP behaviour in the moral norm construct of the TPB.

Belief was also expressed in the nocebo effect and that patients will often have a negative experience with a generic medicine because of the patient’s belief that it is an inferior product. This was held as an additional reason for non-provision of generic alternatives.

A lack of government incentive to encourage generic prescribing was referred to by a majority of GPs as were potentially more complex issues relating to lack of equivalence where the physician may not have the knowledge to be confident about equivalence:

\[\text{...with the uncertainty of the equivalence of bioavailability I tend to go for the proprietary drug or a branded equivalent that I know the exact company that's producing that branded generic, so I have some idea what the patient is getting.}\]

\[\text{If I prescribe generics I have no idea what the patient is getting. (GP17)}\]

Community pharmacists

Pharmacists stated prescribing practices of physicians as one of the primary barriers to increased usage of generic medicines in Ireland (prior to the Health (Pricing And Supply Of Medical Goods) Act of 2013, pharmacists could not substitute and had to dispense exactly as per the prescription).

Similarly to physicians, many pharmacists also stated that patient preference is one of the main barriers to increased usage of generic medicines in Ireland. The main reasons provided for this preference were brand consciousness amongst the general population and the confusion caused by the changing appearance of generic medicines, leading to a general dislike of generics within the patient group.
… how many different [generic alternatives] of Zovirax are out there now? The exact same thing, €3 or €4 cheaper but people say no I want Zovirax because they just think it’s not as good (Ph15)

Furthermore, there were also similar statements from pharmacists relating to the nocebo effect experienced by patients as a result of their lack of confidence in generic medications and how this led patients to request brand name medicines in preference to generic alternatives. Lack of government incentive or interest in generic prescribing was also cited as a barrier (with the influence of the pharmaceutical industry in Ireland again given as a potential reason for this).

Patients
The primary positive behavioural control (which again is consistent with the TPB) expressed by patients was the lesser cost of generic medicines – essentially being able to get the “same thing for at a lower price”.
A majority of the patient group cited lack of knowledge about generic medicines as one of the primary sources of their lack of trust in generics (however a stated trust in medical professionals, primarily GPs, could serve to somewhat negate this barrier). The lack of provision of education and information by the government was also cited as a barrier to use of generics, with one patient stating that is was only “now that the country is broke” that the government became interested in promoting usage of “cheaper alternatives” and in making them more readily available to consumers.
**Non-TPB factors**

As discussed previously, other factors, not consistent with the TPB were noted during data analysis. These were eventually clustered into two areas: the macro context and roles & relationships (see Figure 1 for details).

**Macro context**

Influencers at the macro level were referred to many times by both professional groups (but not by the patient group). These relate primarily to the legislative, policy and political landscapes that impact on medicines provision in Ireland. These are factors that influence at a high level and are likely to be outside the control of the individual while still having an effect on their behaviours. As such, these factors could be considered similar to, and are potentially likely to impact on, the external elements of the PBCs discussed earlier.

GPs expressed concerns that substitution by pharmacists may be influenced by financial incentives rather than clinical motives. This may influence GPs to prescribe branded medication, or to make increased use of the “Do Not Substitute” option in the new legislation. Such factors affecting prescribing practices could have a negative effect on behaviours relating to usage of generic medicines. GP decisions to prescribe the originator brand, and issue instruction to the pharmacist to not substitute, may be influenced by patient preference in addition to GP concern that patients may get confused by the varying appearance of generic medications. Again, this relates to the non-TPB element of negotiation between two parties in relation to behaviours connected to usage of generic medications as well as the moral norm construct (relating to the motivation to help the patient) of the TBP on the part of the prescribing GP.

Many references were also made in the professional groups that compared the situation in the UK to that in the Irish health system, although this was more evident in the
pharmacist cohort than in the GP group. Several of the participants had either trained or spent time working in the UK and commented on how much greater the usage of generics is in the British health system, relative to the Irish system, with no apparent negative impact on clinical outcomes.

*Generic prescribing is done at a much higher rate on the NHS yet is there any greater drug issues, morbidity or mortality arising therefrom? There isn’t. I rest my case. (GP12)*

The greater level of generic prescribing by physicians and acceptance of generic medicines by the general public in the UK was stated as a comparative factor, with many participants querying why a similar situation can’t be successfully implemented in Ireland. This cultural comparison could be seen as being somewhat analogous to the social norm construct within the TPB and might impact on behaviours in that those holding the views expressed are likely to be pro-generic usage and this may influence their peers in the societal norm aspect of the TPB. (Alternatively, it should also be considered that individuals may adopt the local cultural normative behaviours, that is, lack of usage of generics, on return to Ireland).

Concerns were furthermore expressed within the GP group (but not the patient or pharmacist groups) that too much focus on generic medicines might have a negative consequence on innovation and development of new medicines in that reduced amounts of money may be available for research and development within proprietary manufacturing companies. This “social responsibility” factor may be seen as being somewhat analogous to the moral norms construct of the TPB. Such factors may provide a moral dilemma that could impact on physician prescribing behaviours. However, the point is also brought up by stakeholders in all three groups that there is an element of social responsibility to the use of generic medicines. Spending less money
on drugs should mean that money is “freed up” to be used in other areas of the health service, and thus usage of less expensive generics could have the positive effect of improvements for all stakeholders. Again, this factor may impact on behaviours relating to usage of generic medicines as stakeholders my feel compelled by the perceived benefit to society to utilise these less expensive alternatives.
Roles & relationships

Many varying expressions regarding which professional group should be responsible for different aspects of dealing with patients, particularly in relation to informing or educating patients as to the equivalency of generics, were made by both GPs and pharmacists. GPs expressed the view that it’s the pharmacist’s role to explain such things to patients:

*I'm interested in the product that the person gets; I'm not interested in the brand. I leave it to my pharmacy colleagues to enter into a discussion with the patient. I don’t enter into a discussion with the patient regarding the particular brand of product that the patient gets, it’s up to the pharmacist to talk to them about that.*

(GP2)

Conversely, many pharmacists held the opinion that GPs need to spend more time engaging with patients to reassure them about generic medicines.

Given that patients have stated that they are likely to be influenced by members of both professional groups (albeit that GPs appear to have the greater influence), it becomes evident that certain roles, responsibilities and boundaries are present amongst the cohorts. The data in this study show an apparent lack of certainty in these roles and boundaries, therefore there may be scope for engagement amongst professional healthcare groups to clarify and accept responsibility for provision of education and knowledge to patients in such matters.

Furthermore, many within the professional groups point externally to the government and the responsibility that it has to provide education on generic medicines. The view was often stated that the Irish Health Services Executive (HSE) should take a leading role in the provision of education, not only to the general public, but also in the provision of appropriate materials to the professional groups. The intent being to
educate professionals as to the current regulatory processes and procedures but also to facilitate them in the provision of education in as simple and effective a manner as possible, to the patients they deal with on a daily basis.

In fact, improving knowledge of generics within the GP group was a view expressed many times by the pharmacist cohort.

> Sometimes people don’t realise that when you’re in University, doctors actually get very little training on the drugs themselves ... so I think it’s about education really (Ph11)

This is also supported by calls from many of the GPs for education, particularly in relation to how generics are regulated and approved for marketing in Ireland.

Given the close and influential relationship between GPs and patients, and the levels of trust in GPs stated by patients in this study, the opinions of GPs have the potential to greatly influence patient beliefs. Negative opinions held by GPs have the potential to be transferred to patients, thus potentially reducing an already low level of confidence in generic medicines within the patient cohort. As stated earlier, the often-negotiatory nature of this relationship, and the implications for behaviour of patients and GPs, is not consistent with the TPB. It is, however, an important factor to be considered in evaluating behaviours of stakeholders towards generic medicines.
DISCUSSION

The aims of this study were to evaluate the attitudes of healthcare professionals and patients towards generic medicines and to explore the role of other contextual factors that may be important influencers of perceptions and behaviours, using qualitative methodology. This study also compared current perceptions amongst GPs and pharmacists in Ireland to the only existing published information, and showed that there have been substantial changes in favour of generic medicines within these cohorts since 1997. While the professional cohorts are largely positive in their attitudes towards generics, it is worth noting that some reticence remains within the GP group. This attitude has the potential to not only affect the behaviours of members of the cohort, but also to impact on the behaviours of patients, given the strong relationship between patients and GPs and the influence that GP attitudes may have on the “social norm” component of decision making by patients. Indeed, a systematic review of studies using the TPB to investigate shared decision making behaviours in healthcare settings supports this view that the social norm is a key influential factor [40].

Attitudes were primarily assessed using quantitative factors derived from a literature review relating to the areas of quality, safety, efficacy and personal preference. Pharmacists were overwhelmingly positive in their attitudes, whereas patients demonstrated the greatest level of negative opinions regarding generics. GPs’ attitudes were predominantly positive but with some reserve being demonstrated in the areas of efficacy, patient experience with generics and personal preference for proprietary medication (relative to the community pharmacist cohort). Previous research, using the TPB, investigating pharmacist intentions in relation to dispensing specific non-prescription medicines showed that positive attitudes towards the medicine were the best predictor of behaviours to dispense said medicine [41], a situation that is somewhat paralleled in this study.
Another aim was to explore qualitatively other factors that may support understanding the perceptions and behaviours toward generics. In this component we were guided by the TPB and found that moral norms may be more influential than social norms in the prescribing and dispensing of generics (that is, within the professional cohorts). It has been argued that moral norms are a great motivational force, therefore strengthening the intention to adopt a given behaviour [33] and also that the moral norm takes into consideration the ethical dimension of healthcare professionals’ behaviour [34]. In the area of prescribing of statins, however, a recent study using the TPB to explain physician behaviours found that attitudes and perceived controls were better indicators of prescribing intention than were subjective norms [42], which is at variance to what has been observed in this study. The statin-prescribing study [42], however, did not specifically explore moral norms. Therefore, it may be the case that, within the subjective norms construct of the TPB, the influence of moral norms may be more important for prescribing GPs than that of social norms, as this study has demonstrated.

For patients, however, moral norms were not seen to be influential, however the societal belief that low cost equates to inferior quality, as well as the recounted experiences of friends and family members with generic medications were important factors in this group’s behaviours towards generics. This greater impact of attitudes and social norms, relative to PBCs, in patient decision making around healthcare topics is consistent with other similar research, for example: in relation to patient decision making related to sexually transmitted disease testing [43], consumer attitudes towards sodium reduction in foodstuffs [44] and willingness to seek psychiatric help [45]. However, other studies have shown that in other areas of healthcare, such as illness self-monitoring compliance, PBCs as well as subjective norms were important
factors in determining patient behaviours [46]. It is worth considering, furthermore, that social norms may be harnessed in such cases to influence patient behaviours, as this study has shown that patients appear to be strongly influenced by their GP.

Whereas cost was the primary PBC factor for patients in determining behaviour to utilise a generic, many control factors were observed to be important for prescribing and using generics within the professional groups. These included factors that were internal to the individual (such as familiarity with trade names and lack of knowledge of the generic names of medicines) and many which were external to the person and thus perceived as being outside of their control. These included elements such as policy or legislative controls, patient preference and influence of external components such as advertising and the pharmaceutical industry. Interestingly, similar controls on prescribing, perceived by physicians, have been noted in other TBP-based studies - with one study stating that patient expectations were the factor most likely to influence prescribing [31]. Another study which assessed healthcare professionals intentions to use clinical guidelines found that for physicians PBCs were the factor most strongly associated with behavioural intention, whereas for other professionals the subjective norm was seen to be more important [47] which would appear to correlate with the findings of this study, with the exception of the influence of the “moral dilemma” factor in relation to cost of medicines.

This study also found other factors to be important in this context that are not components of the TPB. As stated previously, the addition of such factors is consistent with other research in the healthcare area, which has used the TPB but supplemented the model by recognising that additional variables have an impact on behaviour [36-38]
and ensuring that these additional, non-TPB factors are not neglected, but are given commensurate consideration, in a manner similar to the approach taken in this study. These were clustered into two final groupings that demonstrated that there are factors within the relationships that the cohorts have to each other – with the relationship between GPs and patients being of greater influence on patient behaviours than that between patients and pharmacists. This study has shown an area of potential contentiousness between the professional groups in that there is an apparent lack of clarity in terms of the roles and boundaries linked to patient education on the topic of generic medicines. There may, therefore, be some scope for professional healthcare groups to cooperate with each other, and possibly with other external (e.g. regulatory/government) bodies to clarify the responsibility for engagement with the patient in such matters.

Further factors at a macro level, which have an important impact on behaviours related to usage of generic medicines, were determined to be in the areas of impact on innovation, the legislative and political landscape, the provision of education and cultural comparisons with the UK. These macro-level factors were only seen in the professional groups and were not a consideration for those in the patient group.

Study Limitations

A limitation of the described method could be in the area of participant selection. Contributing GPs had an affiliation with the University of Limerick; as these individuals had some involvement with teaching/training, their mind-sets may differ from those who do not have any link with academia. This argument, however, is somewhat mitigated, as recent research, completed in the same region as these studies, has shown that prescriptions coming from university-affiliated teaching hospitals are almost never written generically [48]. A further potential limitation may be gender and
age balance. However, the GP cohort generally reflects the current situation in Ireland with most established GPs being 40-60 years of age (and the greatest number of these being 50-60 years) and the role currently being dominated by men (approximately three to one).

Participating pharmacists were all community pharmacists, whose opinions may differ from pharmacists working in hospital, or other, settings. Moreover, differing interview settings (some participants were interviewed face-to-face, and others were interviewed over the telephone) might have influenced the data gathered in this study [49]. However, review and comparison of the themes emerging from participants interviewed in different settings did not show any substantial difference in the opinions, perceptions and behaviours expressed between participants in different settings.

While the TPB has been used in investigation of behaviours in many different healthcare fields for many years, recent criticisms [50] have suggested that the TPB has limited predictive validity and that the majority of variability in observed behaviour is not accounted for by measures of the TPB. These criticisms would appear to be upheld by results in this study, which indicate that there are substantial factors, outside the TPB constructs, which appear to be important in determining behaviours towards usage of generic medicines. Furthermore - recent research in the area of implementation of complex medical interventions has also suggested that the TPB may not be an adequate theoretical framework to guide development of questionnaires in this area [51] and that other models may prove more useful.

The theoretical implications of this study are outlined in Figure 2, which shows the TPB constructs which affect intention and thus behaviour, alongside the non-TPB
elements affecting behaviours towards generic medicines, which were elucidated in this study. The relationships and influences between members of the different stakeholder groups are indicated by arrows, the heavier the arrow, the greater the potential influence. This shows the strong patient-GP relationship, and how GPs can influence patient behaviours towards generics both positively and negatively. The still significant, but slightly less important (from the point of view of influencing behaviours of the patient group), relationship between patients and community pharmacists is represented by a lighter arrow. Additionally, there is the potential for members of the two professional groups to influence each other, but this relationship was less evident in the results of this study and thus is represented by the lightest arrow. From this model, we can see that macro context factors have the potential to impact on both TPB and non-TPB mediated behaviours. While some macro context influencers may be outside the control of the individual (e.g., legislative requirements), some (such as cultural comparison and social responsibility, along with its analogous moral norm construct within the TPB) have the potential to influence behaviour at the individual level. In fact, some macro context factors, for example: legislative requirements, will directly mediate behaviour despite any contrary beliefs or influence on the individual.

**RESEARCHER REFLECTIONS**

Research of a qualitative nature, due to the central role of the researcher(s), can have a more subjective element than purely quantitative work. On a personal level, this was one of the most challenging aspects of performing this type of research, as my background – up to that point – had been very much as a quantitative scientist. Moving from performing research where my objective would have been to keep as much subjectivity, and hence myself, out of the work - to a situation where my observations, notes and thoughts would become a fundamental aspect of the work, took a
considerable change of approach – both personally and professionally – in how I performed these studies.

Because of the greater level of involvement of the researcher in this type of study, there is the potential for the researcher’s own biases and preconceptions to influence the work. Therefore, to try to overcome my own predispositions (based on my background and professional experience) I worked with Dr. Stephen Gallagher, who as a health psychologist comes from a very different background to my own, and who provided input into the development of the coding process to prevent my own biases from affecting the outcomes as much as possible.

Early in the process of undertaking these interviews, I became aware of my active, participatory role in the data collection process and how my opinions and biases could affect the manner in which questions were formulated and asked.

With the patient group, I had to make a decision very early in the process, during the first two or three interviews, as to whether or not I should provide an explanation of what a generic medicine is, where participants had shown that they did not have a correct understanding. As my objective in performing these interviews was to garner an understanding of what people actually thought about generics, I felt that it was correct to provide this explanation and did so for all of the interviews – in any case where the participant said they did not know what generic medicines were, or provided an inaccurate explanation when asked that question.

Furthermore, when I was questioning participants about acceptance of generic substitution, I expected to see the most resistance from GMS patients, as they (based on information already given by the pharmacist cohort) tended to be in receipt of more branded medication than private patients. However, when I analysed the data I found that those participants who stated negative opinions about substitution with generic medication, and making of co-payments, were all private patients. This is a good
example of where my preconceptions (and maybe even prejudices) were challenged during these studies.

At the beginning of this project I made a decision that I wanted to carry out this research by interview, rather than the more often used method of questionnaire or survey. I felt, even before I embarked on these studies, that while it would take longer and possibly be more challenging, that the richness of the data gained would make it worthwhile. This undoubtedly was the case and the results have, for me, demonstrated the value of the increased effort. I believe that the work benefited from a more qualitative approach, and I can now say, in retrospect, that I have learned far more from undertaking interview-based research than I would ever have done if I had taken the survey route. My first steps into qualitative approaches to data collection and analysis have shown me that, despite the objective scientific methodology that I learned in my primary and post-graduate degrees, for studies such as these, an active and participative researcher (despite, and even sometimes because of, inherent subjectivity) can add substantially to the data collected and to the richness of the subsequent analysis and interpretation.

CONCLUSION

This study elucidates substantial detail relating to the manifold areas that determine behaviours towards generic medicines in Ireland, within the three cohorts examined. In contrast to the other research in this area, this study has not been limited solely to the investigation of attitudes (as attitudes alone are not the single determinant of human behaviour), but has also uniquely examined other factors that influence behaviours such as social and moral norms and perceived (as well as actual) behavioural controls.
Comparison with existing publications shows that attitudes to generic medicines in Ireland have become more positive over the previous decade and a half, with pharmacists and GPs having become more accepting of, and confident in, their use than had been previously documented. It is not possible to compare patient attitudes as no historical data have been published in an Irish context; however, in this study, patients demonstrate greater reticence to the use of generics than is seen in the professional cohorts.

Theoretical approaches that take other factors into account, such as the TPB, help us to more fully understand decision-making processes and resultant behaviours. This study, therefore, provides for greater understanding of the complex variables that affect behaviours towards generic medications. As such, this research is likely to provide information on areas where future interventions aiming to target improvement of generic medicine usage in Ireland could be focused, to provide enhanced results in terms of changes in behaviour towards acceptance and usage of generic medicines. One such area is in recognising the strong and influential relationship between GPs and patients. Interventions aiming to improve acceptance of generics within the general public may be more successful if they include a component of GP education, as improving GP perceptions is likely to have a positive knock-on effect within the patient cohort.
REFERENCES


Table 1 Quantitative Questions for Assessment of Attitudes

<table>
<thead>
<tr>
<th>Do you strongly agree, agree, neither agree nor disagree, disagree, strongly disagree with the following statements:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Generic medicines are generally of the same quality as originator medicines.</td>
</tr>
<tr>
<td>Generic medicines are generally poorer quality than originator medicines.</td>
</tr>
<tr>
<td>Generic medicines are generally better quality than originator medicines.</td>
</tr>
<tr>
<td>Generic medicines work as effectively as originator medicines.</td>
</tr>
<tr>
<td>Generic medicines work better than originator meds.</td>
</tr>
<tr>
<td>Generic medicines don’t work as well as originator meds</td>
</tr>
<tr>
<td>Generic medicines may be dangerous compared to originator meds</td>
</tr>
<tr>
<td>Generic medicines are as safe as originator meds.</td>
</tr>
<tr>
<td>Generic medicines are manufactured to the same quality as originator medicines.</td>
</tr>
<tr>
<td>Generic medicines are manufactured to a poorer quality than originator meds</td>
</tr>
<tr>
<td>Generic medicines are manufactured to a higher quality than originator meds</td>
</tr>
<tr>
<td>Generic medicines are cheaper to buy than originator meds.</td>
</tr>
<tr>
<td>Generic medicines are cheaper because they are of inferior quality to originator meds.</td>
</tr>
<tr>
<td>If I were ill, I would be happy to take a generic medicine if my doctor prescribed it for me.</td>
</tr>
<tr>
<td>If I were ill, I would prefer to take a originator medicine rather than a generic medicine, even if it is more expensive.</td>
</tr>
</tbody>
</table>
Figure 1: Generation of coding themes for non-TPB factors

- Initial
  - Comparison between Ireland and UK
  - Lack of information/knowledge
  - Responsibly for education

- 1st re-read
  - Cultural or social comparison
  - Provision of education

- Further re-reads
  - Roles and relationships
  - Negotiation between GPs/pharmacists and patients
  - Roles and boundaries of physicians and pharmacists
  - Links/relationships between cohorts
  - Macro level influencers
  - Legislative and political landscape
  - Impact on innovation
  - Social responsibility

- Final
  - Macro context
  - Innovation & social responsibility
Figure 2 Theoretical influencers on behaviours related to usage of generic medicines
Chapter 4

Physician and community pharmacist perceptions of generic medicines: what they think and how they differ.

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Title

Physician and community pharmacist perceptions of generic medicines: what they think and how they differ.

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Abstract

Introduction
With healthcare costs soaring, the Irish government enacted new legislation, in 2013, to introduce generic substitution and reference pricing in Ireland for the first time. No peer-reviewed articles comparing pharmacist and physician opinions about generic medicines appear to have been published in the recent past. Therefore, this novel study is the first comparative assessment of attitudes towards, and behaviours relating to, generic medicines in two primary healthcare professional stakeholder groups – General Practitioners (GPs) and community pharmacists.

Methodology
One-to-one interviews were performed with GPs and community pharmacists. Interviews were semi-structured and included quantitative assessment of opinions using structured questions and a five-point Likert scale response system. Interviews were transcribed verbatim and qualitative analyses were performed using NVivo (version 9). Cronbach’s alpha was calculated to measure the internal consistency of responses from participants to the structured questions.

Results
Perceptions of GPs’ in Ireland towards generic medicines have improved since the last study published on that topic (from 1997). In our study, however, GPs still express more negative opinions, comparatively, than do pharmacists. 91.2% of GPs and 97.7% of pharmacists believed that generics were generally of the same quality as the originator. In terms of efficacy, 11.8% of GPs, compared to only 2.3% of pharmacists, believed generics do not work as well as the originator. High numbers of both GPs (94.1%) and pharmacists (88.6%) reported receiving complaints from patients related to issues with generics and more than twice as many GPs (14.7%) as pharmacists (6.8%) expressed a preference for the originator when taking a medicine themselves.
Discussion

GPs’ relatively negative opinions (compared to pharmacists) could negatively influence patient opinions. Participating healthcare professionals reported a belief that most of the negative experiences (with generic medicines) complained about by patients were not actual but imagined/nocebo, and that patients are resistant to change. Therefore, education of all stakeholders appears to be a fundamental requirement for successful acceptance of increased usage of generic medicines. Moreover, there is a need for resources and supports to enable GPs and pharmacists to easily and quickly educate the general public when appropriate circumstances arise. In addition to educational interventions, altering GP opinions (i.e., countering the negative perceptions observed in this study) may prove an important aspect of successful influencing of patient perceptions.
Introduction

Attitudes towards generic medicines have been studied internationally [1, 2], with many country-specific studies reported including: Australia [3]; Italy [4]; South Africa [5]; Malaysia [6]; Saudi Arabia [7]; Jamaica [8]; France [9]; and USA [10]. However, very few peer-reviewed studies have assessed the attitudes of healthcare professionals in Ireland towards generic medicines. The most recent of these (to the authors’ knowledge), published in 1997, determined General Practitioner (GP) opinions, and showed that the majority of prescribers (75%) were concerned about the reliability and quality of generic medicines [11]. Additionally, a separate 1997 report, which was prepared for the then Irish Minister for Health, stated that over a third of Irish GPs believed that generic medicines were unreliable and of poor quality [12]. Half of the pharmacists surveyed for the report believed that some generic medicines were unreliable, with over 80% of pharmacists reporting patient complaints related to changes in medication, primarily linked with changes to generics. That report also identified that half of the physicians surveyed believed that generic substitution increased patient confusion and a quarter reported experience of patients returning to them with complaints of confusion or dissatisfaction with medication changes.

Historically, Ireland has had one of the lowest rates of generic medicines usage within the EU [13]. Given the low rate of generic medication penetration into the Irish market, and the potential for economic benefit associated with their use, the Irish government has recognised this as a potential area for cost savings. As such, new legislation - the Health (Pricing and Supply of Medical Goods) Act was signed into law in June 2013 [14]. The intent of this legislation is, *inter alia*, to formally introduce the basis for generic substitution and reference pricing in the Irish healthcare system.

With Ireland on the cusp of such major modification in healthcare practices, there are many potential hurdles to be overcome [15]. An assessment and comparison of the
opinions of affected healthcare professionals is not only timely, but also novel. Indeed, the authors could not, in a PubMed search (June 2013), find any peer-reviewed publications (within the last 10 years), comparing pharmacist and physician opinions regarding generic medicines. Therefore, this study has the potential to highlight areas where challenges may arise during implementation of the proposed changes. As the attitudes and behaviours of healthcare professionals may prove pivotal to the successful implementation of the proposed amendments, our objective was to assess the beliefs, attitudes held and behaviours towards generic medicines amongst two of the main stakeholders in the prescribing and dispensing of medicines: GPs and community pharmacists.
Methodology

One-to-one interviews were performed with consenting GPs and community pharmacists between June and October 2012 (either face-to-face or via telephone). GPs affiliated with the University of Limerick’s Graduate Entry Medical School were sent a letter inviting them to participate in the study. Acceptance emails or telephone calls were received from a number of GPs and interview times were arranged. The invitation letter was followed up with a telephone call, 1-2 weeks later, for those GPs who had not already accepted, and interviews were arranged with those who consented to participate. Pharmacists were approached in person, while in the pharmacy, and asked to participate in the study. A verbal explanation of the study was provided, and an invitation letter was offered.

The interviews - which were recorded (with interviewees’ permission) - were primarily semi-structured and based on a series of questions to which open, or qualitative, answers could be given (Table 1). Additional quantitative assessment of opinions was completed using a series of structured, closed questions to which participants could select from pre-defined answers. In this instance, a five-point Likert scale [16] was used, with a single response allowable for each question, selected from: Strongly Agree, Agree, Neutral, Disagree and Strongly Disagree (Table 2). Participants were offered the opportunity to freely express any additional opinions or views at the end of the interview session. The study instrument was informed by a recently published review of the usage of generic medicines and how policy changes to promote the use of generic medicines may affect healthcare provision [13].

Thirty-four (34) GPs and forty-four (44) community pharmacists, from both urban and rural areas, were interviewed. The number of participants in this study is larger than other comparable interview-based studies elsewhere; for example, the only other interview-based investigation of GP perceptions of generic medicines, by Hassali et al in
2006, interviewed 10 GPs [3], and in analogous studies with pharmacists, 16 participants were interviewed for a study in Sweden [17] and six pharmacists (from a total of fifteen healthcare professionals) were interviewed for a similar study in South Africa [5].

Interviews were transcribed and qualitative analysis of responses was performed using NVivo (version 9).

Approval of the design and conducting of this study was granted by the Ethics Committee of the Irish College of General Practitioners (ICGP).

**Statistical Analysis**

Cronbach’s alpha was calculated to measure the internal consistency of responses from participants to the quantitative assessment structured questions (Table 2). A chi-square test was used to measure the association between type of respondent (GP and pharmacist) and level of agreement with the statements combined into three categories (Disagree, Neutral and Agree). A 5% level of significance was used for all statistical tests and no adjustment was made for multiple testing. The statistical software package IBM SPSS Statistics for Windows Version 20.0 was used for analysis.
Results

Participants and setting

Thirty-four (34) GPs and forty-four (44) community pharmacists were interviewed; demographic details are included in Table 3. Quotations from the interviews are shown in Table 4.

For clarity: In Ireland, the General Medical Services (GMS or medical card), scheme is available to persons who are unable, without undue financial hardship, to arrange general practitioner medical and surgical services for themselves and their dependents. Being in receipt of a medical card allows the holder to receive a free (or subsidised) general medical service.

Statistical Analysis

The internal consistency of responses from participants to the structured questions was excellent (Cronbach’s alpha=0.90). There was no significant difference between type of respondent and level of agreement with any of the structured statements except for the following statement:

- “Generic medicines do not work as well as originator medicines” (p<0.001) with a higher percentage of GPs (11.8%) agreeing with the statement compared to pharmacists (2.3%).

Direct comparison of opinions regarding quality, efficacy and safety of generics using structured questions (Table 2)

A majority of participants in both the GP (91.2%) and community pharmacist (97.7%) groups believed that generic medicines were generally of the same quality as the originator (i.e., proprietary) medicine. However, 8.8% of GPs, compared to 2.3% of pharmacists, expressed an opinion that generics were not of the same quality as the originator. Interestingly, with respect to beliefs held regarding efficacy of generics,
11.8% of GPs, compared to only 2.3% of pharmacists, were of the view that generic medicines do not work as effectively as the originator.

70.6% of GPs believed the generic manufacturing process to be of the same standard as that of the originator, compared to 79.5% of pharmacists. Therefore, nearly a third of GPs, and approximately one fifth of pharmacists, expressed a belief that generic medications are not manufactured to the same quality as the originator.

In terms of safety, while all of the pharmacists were of the opinion that generics were as safe as the originator medication, 5.9% of GPs disagreed (with an additional 5.9% not expressing an opinion), arguably indicating that as much as 11.8% of GPs may have held the view that generic medicines are not as safe as the originator.

When asked how they would respond if offered a choice between a generic or the originator, if requiring medication themselves, 14.7% of GPs expressed a preference for the originator – more than double the proportion of community pharmacists who were of the same opinion (6.8%).

**Comparison of GP and pharmacist experiences with generic medicines**

94.1% (32/34) of GPs interviewed had experienced incidents when patients complained that a generic medicine did not work as effectively as an originator medication; 88.6% (39/44) of pharmacists reported similar experiences. (Interestingly, of the five pharmacists who had not experienced this, one community pharmacist stated that he did not deal with generics). Both groups of healthcare professionals reported that negative experiences with generics, as described by patients, tended to be vague and non-specific, such as: the medication did not work as well, the effects wore off more quickly or general feelings of unwellness such as “upset tummy” or headaches.

Pharmacists and GPs additionally stated that patients reported increased or altered side effects when taking generics. Only one of the GPs interviewed, however, mentioned
a serious adverse event, whereby a patient had exhibited an allergic reaction to a red dye present in a generic product that had not been part of the formulation of the originator medicine. In both groups, the healthcare professionals stated that they believed that most of the issues reported by patients were imagined (on the part of the patient) rather than actual. Both GPs and community pharmacists held an opinion, that, in the majority of cases, it was patients’ negative perceptions of generic medicines that led them to have a poor experience with a generic, meaning that, in effect, patients were experiencing a type of nocebo effect.

Medication types associated with complaints were largely common between the two groups, with statins, PPIs, inhalers, antihypertensives and antibiotics being the most often mentioned.

**GP and pharmacist views regarding impact of patient perception**

Both GPs and community pharmacists were of the opinion that patients prefer the first medicine introduced to them, and that patients are resistant to change. This is exemplified by the fact that 25% (11/44) of pharmacists and 20.6% (7/34) of GPs reported situations where patients complained that an originator medication did not work as well as a generic. In most of these cases, the generic had been the first medication received by the patient. The GPs and pharmacists believed that it was the change in medication that led the patient to have an issue, rather than a problem with the medication itself.

Both GPs and pharmacists stated that, in a majority of cases relating to patient complaints about generics, they acquiesced to the patient’s wishes and subsequently prescribed/dispensed the branded medication. Only 26.5% of GPs (9/34) or 20.5% of pharmacists (9/44) stated that they had attempted to educate the patient as to the equivalency of the medicines. In fact, one GP reported making such an attempt to
educate a patient and did not capitulate to the patient’s demands to have the originator medication prescribed for them. As a result, the patient left that practice. Conversely, one of the pharmacists described a similar discussion with a patient regarding a complaint about an inhaler. In that case, the pharmacist presented both the proprietary and generic inhalers to the patient, and showed the patient the ingredients list, to prove that the active ingredients were identical. Seeing both inhalers persuaded the patient to try the generic inhaler.

**Opinions regarding low levels of generic usage in the past**

When asked about their opinions as to why usage of generics in Ireland has been low historically, the provided reasons common to the two groups included: the influence of the (proprietary) pharmaceutical industry, including interactions with medical representatives; lack of generic prescribing, including the lack of any government incentive for GPs to prescribe generically; poor cost consciousness; poor education regarding generics and, consequently, poor understanding of generics by consumers; brand consciousness or loyalty on the part of the consumer and the non-allowance of generic substitution. Pharmacists and GPs both stated that patients exhibited a strong preference for branded medication.

Both community pharmacists (22.7% - 10/44) and GPs (44.1% - 15/34) expressed a view that different aesthetic presentations of generic medicines were a disadvantage associated with their use, reporting that this caused issues of confusion and medication errors for some people, particularly elderly patients and those on long-term medication. This reason was given by GPs as one of the primary reasons for continued prescribing of the proprietary brand once a generic alternative had been introduced to the market. Interestingly, however, 32.4% (11/34) of GPs and 4.5% (2/44) of pharmacists interviewed, when asked what their understanding was of how a generic medication
differs from an originator medicine, stated that there was no difference – disregarding aesthetic variation (i.e., visual or packaging difference). Additionally, they made no reference to the fact that excipients may vary considerably between the originator medication and generic equivalents.

**Opinions regarding branded generics**

An interesting divergence of opinion was noted in the area of branded generics. GPs expressed positive opinions about branded generics, indicating that they believed them to be reputable and trusted sources of generic medications, in addition to the fact that they may have an awareness of where the branded generic was manufactured and knowledge of how it had worked for patients in the past. Conversely, community pharmacist opinions of branded generics tended to be less positive, with opinions expressed including themes such as: branding of generics being counterintuitive and to some extent negating the reason for having generic medications; that branded generics required them to stock multiple types of the same generic medication and that branding of generics should be stopped and not permitted by the pharmaceutical regulators.

**Views held regarding education and awareness of impending changes**

Education of consumers was seen, by both groups, as a necessary step for wider acceptance of generics and to overcome the perception by some patients that generics are sub-standard due to being less expensive; the so-called “own-brand syndrome”.

While all of the community pharmacists interviewed had some level of awareness of the proposed legislative change, just over one quarter (26.5% - 9/34) of GPs were unaware (at the time of interviewing) of the Irish government’s plans to introduce new legislation for generic substitution and reference pricing.
DISCUSSION

In the context of deriving successful strategies for usage of generic medicines, this study of healthcare professionals’ attitudes towards generics provides insight into the potential hurdles that may need to be overcome in enabling acceptance of generics by healthcare professionals and consumers/patients alike. Previous studies have looked at physician [3, 8, 18] and, to a lesser extent, pharmacist opinions about generic medicines [17], but there is a gap in the literature as no recent comparison of the opinions of General Practitioners and community pharmacists could be found. In fact, the authors were unable to identify (in a PubMed search performed in June 2013) any publication dealing with this topic in the prior 10 years.

The most recent study published which determined Irish GP attitudes towards generic medicines [11] found that 75% of prescribers were concerned about the reliability and quality of generic drugs. That attitude, expressed in 1997, contrasts greatly with the GP opinions expressed in this study, where over 91% of GPs interviewed stated their confidence that generics are of comparable quality to originator medications. This clearly indicates that a considerable shift in the views of general practitioners has occurred in favour of generic medicines. While no previous peer-reviewed publications exist which give a historical perspective on the perceptions of pharmacists in Ireland towards generics, a report from 1997 (for the then Irish Minister for Health, on a previous attempt by the Irish Government to improve use of generics [12]) stated that about of half of pharmacists believed that some generic drugs were unreliable. This, again, is in complete contrast to the findings of our study and indicates a significant change in the opinions of pharmacists in the intervening time period.

A minor disparity in opinions about the safety of generics was noted during this study. A small number of GPs (6%) held the belief that generics were not safe relative to originator medicines. However, the complexity of this view is apparent, as the GPs
involved did not necessarily indicate a lack of confidence specifically related to the manufacturing, constituents or quality of generic medications. Rather, they expressed views regarding the unsuitability of equivalence of generic substitution for some narrow therapeutic index (NTI) drugs, such as some antiepileptic drugs, and the fact that excipients may differ between the originator and equivalent generic formulations. Interestingly, as all of the community pharmacists were of the opinion that generics were as safe as the originators, this may indicate that the factors influencing GPs, described above, were not being considered by pharmacists as a source of potential risk associated with usage of generics.

Furthermore, given that about one third of GPs (compared to less than 5% of pharmacists) may be unaware that only the active ingredient must be identical between an originator medicine and equivalent, interchangeable generics, this may represent a potential area for educational interventions for GPs. Differences, not only in appearance and taste of the medicine (which would be immediately apparent to the consumer) but also in the excipients used, could be the source of potentially serious issues for a patient, such as the previously cited example where a patient had an allergic reaction to a dye. Indeed, evidence has been published that differences in excipients between originator medications and their generic counterparts can cause problems [19, 20].

In fact, the theme of education was raised repeatedly in the interviews conducted during this study. Both community pharmacists and GPs held the belief that adequate and focussed education – of both healthcare professionals and the general public – in relation to generic medicines, constitutes an essential aspect of their acceptance and improved use. While all of the pharmacists had some knowledge of the legislative change intended by the Irish Government in the new Health (Pricing and Supply of Medical Goods) Act (2013), nearly one third of GPs were not aware of it. This indicated
that, for successful implementation of the new legislation within the Irish health system, education efforts should focus to some degree on prescribers. A significant disadvantage to the use of generics – and a factor identified as conducive to continued use of proprietary medicines - was variability in appearance of generics. Differences in shape, size, colour, appearance, taste etc. can lead to confusion, lack of compliance and medication errors in elderly patients or those on long-term medication. Patient education is likely to be the simplest and most time effective solution to this issue. In fact, this study has shown that patient preference, to a large degree, dictated prescribing and dispensing practices. Both pharmacists and GPs stated that, in most situations where a patient complained about having an issue with a generic medication, they acquiesced to the patient’s wishes, without attempting to educate them. If patients are not adequately informed and educated, there is a strong likelihood that the new system will meet with significant opposition and possibly failure - including a potential increase in patient non-compliance with medication and/or medication errors caused by such confusion. Moreover, support is needed for the Irish pharmacist and GP groups, in the form of an educative intervention (website, pamphlet, information leaflet, etc.) to aid them in quickly and clearly providing good quality, clearly understandable and unbiased information to patients. With the advent of the proposed introduction of generic substitution and reference pricing in Ireland, this may be of benefit in improving overall perceptions of generics in the marketplace. This could be facilitated, for example, by use of a novel tool, recently published by our group, based on optimised quality of information and reading ability, for development of websites providing healthcare information that could be utilised in the provision of such supports [21]. This study showed that GPs tend to hold, comparatively, a more negative opinion of generics than do community pharmacists. Given the pivotal role that the GP plays in drug prescribing, a question is raised as to the impact of this relatively negative
opinion on patients. If the prescribing GP holds a negative opinion, how – given the influence that the physician may have on the placebo/nocebo effect [21] – will that opinion influence patient opinion and acceptance of generic medications? While there are many opinions as to why Ireland has had a poor track record of usage of generics, implementation of the proposed legislation will bring the Irish procedures on a par with many other systems for drug dispensing worldwide. Improving of GP opinions, including countering any negative perceptions held, could be fundamental to a successful increase in the use, and acceptance, of generic medicines.
Acknowledgements

This work was supported in part by a scholarship from the Faculty of Education and Health Sciences, University of Limerick, Ireland.

The authors wish to express their sincere thanks to all of the GPs and pharmacists who took part in these interviews.
Table 1: Study Instrument: questions that formed the basis for semi-structured interviews

<table>
<thead>
<tr>
<th>Question</th>
<th>Details</th>
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<tr>
<td>What is your understanding of what a generic medicine is?</td>
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<tr>
<td>What is your understanding of how a generic medicine differs from an originator medicine?</td>
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<tr>
<td>What is your understanding of bioequivalence?</td>
<td>To the best of your knowledge, what percentage difference is allowed in terms of bioequivalence between an originator medicine and an equivalent generic product?</td>
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<tr>
<td>What is your understanding of why generic medicines are cheaper than originator medicines?</td>
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<tr>
<td>What do you believe about how generic medicines compare to brand-name medicines?</td>
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<tr>
<td>What is your opinion as to why use of generic drugs in Ireland has historically been much lower than other European countries?</td>
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<tr>
<td>Have you ever had a patient report that a generic medicine, which you prescribed/dispensed for them, didn’t work as effectively as an originator medicine?</td>
<td>If yes, what type of medicine(s) have you seen this with? If yes, can you please give some brief details of what the patient reported having experienced? What action did you take in this case? Did you then prescribe/dispense the originator medicine? If yes, was there any reported lack of efficacy from the substituted originator medicine?</td>
</tr>
<tr>
<td>Have you ever had a patient report that an originator medicine, which you prescribed/dispensed for them, didn’t work as effectively as a generic medicine?</td>
<td>If yes, what type of medicine(s) have you seen this with? If yes, can you please give some brief details of what the patient reported having experienced? What action did you take in this case?</td>
</tr>
<tr>
<td>Are you aware of the government’s proposed plans to introduce reference pricing and generic substitution in Ireland?</td>
<td>What is your opinion of this proposed change in Irish legislation?</td>
</tr>
<tr>
<td>Questions asked specifically of GPs</td>
<td></td>
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<td></td>
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<tr>
<td>Do you actively prescribe generic medicines?</td>
<td></td>
</tr>
<tr>
<td>Do you ever prescribe generic medicines in preference to originator medicines?</td>
<td></td>
</tr>
<tr>
<td>If yes, please explain why.</td>
<td></td>
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<tr>
<td>Do you ever prescribe originator medicines in preference to generic medicines?</td>
<td></td>
</tr>
<tr>
<td>If yes, please explain why.</td>
<td></td>
</tr>
</tbody>
</table>
Table 2 – Study instrument: structured questions and comparison of GP and pharmacist responses.

<table>
<thead>
<tr>
<th>Do you strongly agree, agree, neither agree nor disagree, disagree, strongly disagree with the following statements:</th>
<th>GPs n=34</th>
<th>Pharmacists n=44</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SA/A(^1)</td>
<td>SD/D(^2)</td>
</tr>
<tr>
<td>Generic medicines are generally of the same quality as originator medicines.</td>
<td>31 91.2</td>
<td>3 8.8</td>
</tr>
<tr>
<td>Generic medicines do not work as well as originator medicines.</td>
<td>4 11.8</td>
<td>27 79.4</td>
</tr>
<tr>
<td>Generic medicines are as safe as originator medicines.</td>
<td>30 88.2</td>
<td>2 5.9</td>
</tr>
<tr>
<td>Generic medicines are manufactured to the same quality as originator medicines.</td>
<td>24 70.6</td>
<td>5 14.7</td>
</tr>
<tr>
<td>Generic medicines are cheaper because they are of inferior quality to originator medicines.</td>
<td>1 2.9</td>
<td>32 94.1</td>
</tr>
<tr>
<td>If I were ill, I would prefer to take an originator medicine rather than a generic medicine, even if it is more expensive.</td>
<td>5 14.7</td>
<td>23 67.6</td>
</tr>
</tbody>
</table>

\(^1\)Strongly Agree/Agree  
\(^2\)Strongly Disagree/Disagree  
\(^3\)Neutral/No opinion
Table 3 – Demographics of interview groups

<table>
<thead>
<tr>
<th>Group</th>
<th>Gender</th>
<th>Age</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M</td>
<td>F</td>
<td>18-29</td>
<td>30-39</td>
<td>40-49</td>
<td>50-64</td>
</tr>
<tr>
<td>GPs n=34</td>
<td>28</td>
<td>6</td>
<td>0</td>
<td>4</td>
<td>10</td>
<td>20</td>
</tr>
<tr>
<td>Pharmacists n=44</td>
<td>23</td>
<td>21</td>
<td>9</td>
<td>17</td>
<td>10</td>
<td>5</td>
</tr>
</tbody>
</table>
### Table 4 – Quotations on themes from GPs and pharmacists

<table>
<thead>
<tr>
<th>Theme</th>
<th>GP quotations</th>
<th>Pharmacist quotations</th>
</tr>
</thead>
</table>
| Prescribing & Dispensing of medicines | There probably should be a lot more incentive, I would even go so far as to say a little bit of compulsion on us, to prescribe more generically. Male, aged 50-64 years.  
The reps are on the road all the time here and I don’t know why we tolerate it really. It must have an effect, the number of guys who are coming in. Some of the pharmaceutical companies are really good on education and things like that. Obviously there are problems with the quality of information ... they give you the information to make you bend in their direction. We have tended to rely on them for education. Male, aged 50-64 years.  
I’m in a practice where we don’t actually see medical reps, but there’s still very strong advertising of non-generic meds. There isn’t anything like the same information on generics. So there isn’t the same familiarity with generic drugs as there is with the branded ones. Even if you don’t see [pharmaceutical representatives] it’s amazing how much stuff still gets into your surgery with brand names on it. I think that’s the main reason why we don’t prescribe generics. Female, aged 40-49 years.  
I’m interested in the product that the person gets I’m not interested in the brand. I leave it to my pharmacy colleagues to enter into a discussion with the patient, I don’t enter into a discussion with the patient regarding the particular type of product that the patient gets, it is entirely up to the pharmacist to talk to them about that. Male, aged 50-64 years. | A lot of the time [GPs] just don’t know that there’s [a significant price difference] - like an antibiotic, let’s say Zithromax, there could be possibly €10 in the difference with the generic, [GPs] just don’t know that themselves, so I suppose there’s a bit of work to be done on that side as well...it would be nice for [GPs] to have the pricing information as well, to just go ‘I know John is out of work, and is still a private patient, so lets generically prescribe’ or to just write in: please give cheapest or best value product. Female, aged 30-39 years.  
They shouldn’t allow generic companies to introduce brand names on their medicines, there should be the name of the manufacturer on the packet but they should just have the generic name on it. Male, aged 30-39 years. |
| Impact of change to a generic medication | When you write a generic [prescription] and the patient gets a different brand to what they got last month and they’re ringing up saying they didn’t get their usual tablets. Male, aged 50-64 years.  
I think it’s going to be very difficult at pharmacy level if the colour and shape of the tabs is going to change every month, which | [Patients] just want the same [the originator they had previously], and then you try to explain to them that it is exactly the same thing and they just say: ‘it doesn’t do anything for me’. Female, aged 30-39 years.  
People don’t want to change, they’ve got their branded drug and they don’t want to |
will lead to medication errors and thus increased hospital admissions, particularly among the elderly, and therefore savings might not be as high. Male, aged 50-64 years.

When you ask the patient “are you taking your Losec?”, they say “I’m not taking Losec” and when you look at it they’re taking omeprazole generic equivalent which you might not be familiar with - so it causes a lot of confusion when you prescribe a proprietary drug and the generic is dispensed. Male, aged 50-64 years.

<table>
<thead>
<tr>
<th>Comparison of generics and originator medications</th>
<th>I'm very much in favour [of generics], I believe they compare very well. I don't see any great difference between generics and brands. Male, aged 40-49 years.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>What would have me concerned is when you look at anticonvulsants and they're not happy to have them substituted, and there's a fairly significant difference between warfarin - that makes you think any time we have any real evidence about bioavailability or bioactivity or whatever the word is used, you see there's a chance that they're not really the same thing at all. (laugh) so my suspicion is that ... they're the same but in the absence of knowledge, you begin to suspect that they are inferior, which is probably not true. Male, aged 50-64 years.</td>
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<td></td>
<td>The pharmaceutical industry is very powerful, and I think that if there was something really against generics they would have found it and used it. A lot of people on the public health side of things won't allow for the possibility that they may be inferior, and that's a problem. And I think that we need to be properly scientific about it. Male, aged 50-64 years.</td>
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<td></td>
<td>We received a phone call from a consultant neurologist asking us not to prescribe generic carbamazepine because she had noticed differences in the serum levels of patients prescribed generically compared to the original product, under her guidance we’ve had to go back prescribing the original. So that was the only, the strongest [experience] against generics that I’ve had. Male, aged 40-49 years.</td>
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<td></td>
<td>I would have some concerns about sources of generics. Generics imported from abroad being of poor quality...I have had patients come in recently, not asking me to prescribe generically, but asking me to prescribe a</td>
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<td>change, it’s what they’re used to. Female, aged 30-39 years.</td>
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<td></td>
<td>I have had one patient who we started on one generic and was determined to stay on that specific generic rather than be changed. Change is something people are very adverse to, changing box or from one generic to another is something that people don’t like. Male, aged 40-49 years.</td>
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<td></td>
<td>How they compare? I think they’re pretty identical, I think they would have the same, the same action [but] I would have customers coming in and saying that [named generic medicine] doesn’t work for them but [brand name drug] does but I think it’s more psychological than [actual]. Female, aged 18-29 years.</td>
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<td></td>
<td>I think sometimes [generic medicines are] not as polished, I’d say like as in I’m sure the standards are correct but sometimes like the coating isn’t as good, the tablet wouldn’t be as good as you’d expect. Female, aged 18-29 years.</td>
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<td></td>
<td>There are some generics where say if [the pharmacist is] doing up a blister pack for people, when we knock them out ourselves and put them in dosage packs, sometimes the tablet just crumbles when you pop it out so it’s down to poor binding agents, maybe the quality might be poor in some cases, but generally they’re quite good. Obviously some customers just don’t like them; they’re used to their brand. Female, aged 18-29 years.</td>
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<td></td>
<td>In practice most of them are fine with patients, from time to time you will have issues where different colours or different constituents might cause problems and reactions in patients that they didn’t have with the original medicine, mostly they are fine. Male, aged 18-29 years.</td>
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<tr>
<td></td>
<td>I don’t think like the standard of tablet is poorer but I do think the packaging of generics is inferior but I’m happy enough with the tablet that’s inside. Female, aged 30-39 years.</td>
</tr>
<tr>
<td>Patient perceptions of generics</td>
<td>Specific branded generic, prompted by the pharmacist. Male, aged 50-64 years.</td>
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<td>-----------------------------------------------------------------------------</td>
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<tr>
<td>...the patient reported that the packaging looked different and the feeling was that they were getting an inferior product. That was their assessment of it and they weren’t happy with that. Male, aged 50-64 years.</td>
<td>It’s a perception, a psychological thing that because [.generics are] cheaper that [patients believe] they wouldn’t be as effective. Female, aged 30-39 years.</td>
</tr>
<tr>
<td>There’s a perception with the patient that the chemist is trying to save money or giving them the cheap drug and claiming for the more expensive one, so there’s a lot of work that has to be done in convincing people that generics are ok. And I think that some work has to be done in convincing GPs that generics are ok because I have seen relatively frequently - once, twice, three times per month people have taken a generic and have had some problem with it, either an actual or perceived side effect. Male, aged 50-64 years.</td>
<td>I had a situation where [a patient] got the parallel import originator and they were complaining that it wasn’t the Irish pack and they brought back in their old pack and it was actually from a different parallel import company – so it was the exact same product just different packaging. Male, aged 30-39 years.</td>
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<tr>
<td>... another patient would only take augmentin for diverticulitis and she was absolutely adamant that it was only augmentin that would work: “I have co-amoxiclav, but it wasn’t as good” (patient speaking) and she was certainly not happy. [Under] a lot of pressure from her and I did give in and just give augmentin. Female, aged 50-64 years.</td>
<td>I think as well that [patient opinions of generics] will vary from place to place because, say, here a lot of our customers are medical card holders and their level of education wouldn’t be as good as it would be in [a more affluent area] or somewhere like that. There’s a level of because they’re [from a poorer area] and because they get [their medication] on the medical card, that they’re being treated badly, so I think it’s a social thing and it’s an educational thing. Female, aged 40-49 years.</td>
</tr>
<tr>
<td>... there was a suspicion certainly from patients that you were giving them a cheaper product because you were trying to save money. Male, aged 50-64 years.</td>
<td>One person told me they felt … their cholesterol had gone up so they chose to go back to the original brand of cholesterol medicine. Female, aged 30-39 years.</td>
</tr>
<tr>
<td><strong>Education</strong></td>
<td>There’s also pressure put on doctors from patients that the generics aren’t as good as the originator and probably we’re not good enough at explaining to patients that really it’s the same thing. Male, aged 40-49 years.</td>
</tr>
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<td></td>
<td>Each patient should be spoken to when there is a medication change so that they know exactly what’s happening, because there’s nothing more infuriating from their point of view than going home, opening the bag and the pink tablet is now a white tablet or whatever. It’s really up to the [health service provider] to try and communicate it to patients, it’s up to doctors and pharmacists to do it at a local...</td>
</tr>
<tr>
<td><strong>New legislation</strong></td>
<td>I think that reference pricing is necessary full stop. Male, aged 50-64 years.</td>
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<td></td>
<td>I think that if reference pricing comes in there needs to be a huge educational campaign that this is not a negative thing in relation to effectiveness of treatment and this is a positive thing in relation to cutting costs which I think everybody is a aware needs to be done. Male, aged 50-64 years.</td>
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<td></td>
<td>generics are] not grossly inferior but you would like to have the choice of prescribing the originator. Male, aged 50-64 years.</td>
</tr>
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<td></td>
<td>I can envisage that people will have problems, because we've had issues before with people and when it does come to it, I'd say a lot of people won't be happy with taking the generic one or whatever one is the best price at the time, because they're just comfortable taking their one particular brand and that's it, they want to stick with it. Female, aged 30-39 years.</td>
</tr>
</tbody>
</table>
References:


Chapter 5

Beliefs, perceptions, and behaviours of general practitioners towards
generic medicines.


Citation:

1. Title:
Beliefs, perceptions, and behaviours of general practitioners towards generic medicines.

2. Qualitative Research

3. Authors:
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6. Abstract

Background
To benefit from the cost-savings associated with use of generic medicines, Ireland has recently introduced generic substitution and reference pricing. The attitudes and behaviours of healthcare professionals are pivotal to the successful implementation of such changes.

Objectives
To assess the perceptions of generic medicines amongst General Practitioners (GPs); to determine what influences may be exerted as a consequence of the opinions of this stakeholder group.

Methods
One-to-one interviews were performed with 34 GPs affiliated with the Medical School at the University of Limerick. Interviews were semi-structured and included quantitative assessments of opinions. Interviews were transcribed and qualitative analyses were performed using NVivo (version 9).

Results
88% of GPs prescribe generic medicines actively. Over 90% believed that generics worked as effectively, and were of the same quality, as originator medicines. 94% of GPs reported receiving patient complaints regarding generics; 29% reported complaints of increased or altered side effects. 94% of GPs stated that they would take a generic, although 15% would choose the originator if offered a choice. Almost 12% were of the view that generics are manufactured to a poorer quality than originators.

Conclusion
This study, the first since 1997, of GPs’ attitudes towards generics in Ireland, highlights that this key stakeholder group have positive attitudes towards both generics and the legislation. Concerns regarding patient experience, clinical
effectiveness and manufacturing quality were identified and these should be addressed in interventions supporting the implementation of the new legislation.

7. Keywords

Generic drugs, general practitioners, perception, patient education, professional education, qualitative research.
8. Main body

Introduction

In June 2013, Ireland signed a new Act into law (the Health (Pricing and Supply of Medical Goods) Act 2013) [1], paving the way for generic substitution and reference pricing for the first time in that market. As a consequence of this new legislation, Irish patients are now more likely than ever to receive a generic medicine. The opinions of General Practitioners (GPs) are a key influencing factor on the views that patients exhibit towards generic medicines [2]. Said influence, in addition to their own role as prescribers, means that GP perceptions are important for the successful implementation of the proposed changes; that is, to increase the use of generic medicines in Ireland. Despite this, to the authors’ knowledge, the most recent peer-reviewed publication on this topic, from Ireland, dates from 1997 [3]. Moreover, a PubMed search (June 2013) showed seventeen publications internationally in the last ten years, on the topic of physician perceptions of generic medicines (six of which were not in English) - only seven of which were specifically related to general practitioner opinions [4-10] (four of which [5, 8-10] were not in English).

The most recent paper on Irish GP perceptions of generic medicines, from 1997 [3], stated that a majority of prescribers (75%) had concerns about the reliability and quality of generics. Additionally, a 1997 report, (prepared for the then Irish Minister for Health on a previous attempt by the Irish Government to increase usage of generic medicines), stated that over a third of Irish GPs believed that generic medicines were unreliable and of poor quality [11]. That report also identified that half of the physicians surveyed reported that generic substitution increased patient confusion and a quarter reported patients returning with complaints of confusion or dissatisfaction with changes in their medication.
With Ireland on the cusp of a major modification in healthcare practices, there are many potential hurdles to be overcome [12]. To determine what influences may be exerted as a consequence of the opinions of this critical stakeholder group, this study assessed the beliefs and attitudes held, in addition to the behaviours towards, generic medicines amongst GPs - as representatives of prescribing physicians in Ireland - in the time leading up to the enactment of the new legislation.
Methodology

GPs affiliated with the University of Limerick’s Graduate Entry Medical School were invited by letter to participate in the study. Acceptance emails or telephone calls were received from a number of GPs and interview times were arranged. The invitation letter was followed up with a telephone call, 1-2 weeks later, for those GPs who had not already accepted, and interviews were arranged with those who consented to participate. One-to-one interviews were carried out with consenting participants between June and August 2012 (either face-to-face or via telephone). Interviews, which were recorded (with each interviewee’s permission), were primarily semi-structured and based on a series of questions to which open, or qualitative, answers could be given (Table 1). Additional quantitative assessment of opinions was completed using a series of structured, closed questions to which participants could select from pre-defined answers (Table 2). In that instance, a five-point Likert scale was used with a single response allowed for each question, selected from: Strongly Agree, Agree, Neutral, Disagree and Strongly Disagree. Participants were offered the opportunity to freely express any additional opinions or views at the end of the interview session. The study instrument was informed by a recently published review of the usage of generic medicines and how policy changes to promote the use of generic medicines may affect healthcare provision [13].

Interviews were transcribed and analysis of responses was performed using NVivo (version 9).
Results

Participants

Thirty-four (34) GPs, from both urban and rural areas, were interviewed (representing approximately 1.4% of the circa 2,500 GPs in Ireland). Interviewee group demographics: 28 male/6 female. All participants were between the ages of 30 and 64 years, with the following age profiles: 18-29: 0; 30-39: 4; 40-49: 10; 50-64: 20; 65+: 0.

The number of participants in this study compared favourably with the only interview-based study that could be found - a study of GPs’ views of generic medicines by Hassali et al in Melbourne, Australia [14] - which used interviews with 10 GPs.

GP behaviours regarding generic prescribing

A majority of GPs, 88.2% (30/34), stated that they prescribe generic medicines actively and that, in general, they prescribe generics in preference to originators. While the primary reason stated for this was the reduced cost, other reasons given included: being in a practice, or having a personal ethos, that was pro generic prescribing; patient preference for a generic; being more familiar with the generic name; and knowledge/awareness of employment provided by generic medicines manufacturers in Ireland. A relevant quotation provided by a GP is:

- My attitude would be that as long as the product has the appropriate approval by the regulatory authorities in Ireland ... that with a few exceptions, and by exceptions I would talk about a few anti-epileptic preparations and warfarin preparations ... generic preparations are so similar as to be the same ... entirely interchangeable. GP2, male, aged 50-64 years.

82.3% (28/34) of GPs stated that there are times when they would preferentially prescribe the originator over an equivalent generic. These situations included: requirement for narrow therapeutic index drugs and those which are not readily
interchangeable (e.g., some anticonvulsants and anticoagulants, etc.); habit, combined with being more familiar with proprietary (i.e., trade) name, thus facilitating prescribing; patient preference or request; variability in the presentation of generics and the potential for this to cause stress or confusion for patients; the originator being same price or cheaper than the generic; holding an opinion that originator was better (having had more experience with, or trust in, the originator medication); and having had experience with poor (or “cheap”) packaging of generics.

**GP opinions regarding quality and efficacy of generics (Table 2)**

91.2% of GPs (31/34) believed that generic medicines were generally of the same quality as the originator medicine. Likewise, 91.2% believed that generics worked as effectively as originators, being equivalent to the originator, although 2.9% of GPs did not hold this opinion. Indeed, 11.8% of GPs (4/34) stated that, in their opinion, generics may be dangerous compared to the originators.

-... [generics and originators] compare very well. For example I’m on a generic statin versus the originator statin and I’m just as well off on it. GP12, male, aged 50-64 years.

- there’s a chance that they’re not really the same thing at all ... my suspicion is that they’re the same, but in the absence of knowledge, you begin to suspect that they are inferior... GP13, male, aged 50-64 years.

Regarding production of generics, 70.6% of GPs (24/34) believed that generic manufacturing is of the same standard as that of the originator. However, 11.8% held the view that generics are manufactured to a poorer quality than originators. Tellingly, while 94.1% of GPs said that they would take a generic medicine themselves, 14.7% of GPs expressed a preference for an originator brand, when offered a choice between the originator and a generic, even if more expensive.

**GP experiences with patient complaints related to generic medicines**
94.1% (32/34) of GPs reported having received patient complaints regarding generics. Where a patient reported a negative experience with a generic, GPs stated that the patients primarily complained of complete or partial lack of efficacy (e.g., inhaler effect wearing off sooner etc.). Furthermore, 29.4% of GPs (10/34) reported that patients had complained of altered or increased side effects when taking a generic.

In 87.5% (28/32) of the cases above, GPs reported that they subsequently prescribed the originator medicine for the patient.

- *I give them what they want. It is pointless arguing.* GP26, male, aged 50-64 years.

- *... if they had had the brand name medicine previously and it worked well for them, I'd put them back on that if that's what they wanted.* GP29, female, aged 50-64 years.

Without exception, no further reports of lack of efficacy/continuing issues were received by the GP from patients subsequent to prescribing of the originator. It is not surprising then that only 26.5% (9/34) of GPs reported any attempt at educating/persuading the patient as to the equivalency of generics. Conversely, 20.6% (7/34) of GPs reported having experienced patients describing how originator medication did not perform as well as a generic. In that scenario, GPs reported that the patient had, in most cases, received the generic first and subsequently switched to the originator. Thus, their preference was for the medication they were first exposed to.

- *Patients are fickle...different size, colour of tablet makes all the difference.*

  You can have people having one branded generic and actually liking it and then it’s out of stock and the chemist gives them a different branded generic and they don’t like that one, or it doesn’t work. But I do believe that these are just issues of belief, really rather than any actual difference between the tablets. GP8, male, aged 40-49 years.
32.4% (11/34) of GPs expressed the opinion that patients are prejudiced against generic medicines, leading to a nocebo effect; hence that patient complaints about generics are often imagined rather than actual.

- There’s a huge placebo effect with any medication; patient belief is very hard to measure. You’ll get people who’ll take one tablet of something and tell you it doesn’t suit - that they felt their blood pressure was rising and impossible things to gauge - when people have these beliefs it’s very hard to work against that. GP8, male, aged 40-49 years.
Knowledge and opinion of proposed legislative changes

73.5% (25/34) of GPs were aware of the Irish Government’s plans to introduce new legislation for generic substitution and reference pricing, with an additional 11.8% (4/34) being vaguely aware. 14.7% (5/34) had no awareness of the proposed changes. With regard to the new legislation: 56% (19/34) expressed a positive opinion. However, 26.5% of GPs (9/34) expressed a desire to retain the option to prescribe originator medicine and not have it substituted (which is allowed for in the Act, to facilitate optimised patient care based on physician discretion and experience with specific patient need).

Other opinions of generic medicines

Branded generics were favoured by GPs as being a reputable source of generics; GPs held the view that they can have knowledge of the product in terms of where it is manufactured and how it has worked in the past relative to other (non-branded) generic preparations.

"...with the uncertainty of the equivalence of bioavailability I tend to go for the proprietary drug, or a branded equivalent where I know the exact company that’s producing the branded generic, so I have some idea what the patient is getting. If I prescribe by generic I have no idea what the patient is getting." GP17, female, aged 50-64 years.

Substitution by the pharmacist, however, was mentioned as a potential issue in this regard (26.5% - 9/34 GPs), although 17.6% of GPs (6/34) believed that pharmacist decisions on what to dispense may be based on profit margins. The disconnect between what is prescribed and what is eventually dispensed, and the impact that this potential change could have on patients, was also a concern expressed by some GPs.

Generally supportive of generic substitution, 35.3% of GPs (12/34) were of the view that no more money than is necessary should be spent on medications. The rising cost of new
medications was referred to, as were cost-savings achievable by increased use of generics and the potential for those to contribute to the funding needed to improve the availability of such new treatments. Only a small number of GPs (11.8% - 4/34) referred to the potential for any impact on research and development that may be brought about by increased usage of generics.

Education

Lack of knowledge, or the requirement for education on the topic of generics, for both of GPs and patients, was a recurring theme. That requirement was reinforced by the fact that while a majority of GPs (91.2% - 31/34) could provide a correct explanation as to what a generic medicine was, none knew the bioequivalence tolerance limits for generics as set by pharmaceutical regulators involved in generic drug approvals (although the majority, 88.2% (30/34), could provide a correct explanation as to what bioequivalence was).

A number of GPs (17.6% - 6/34) also expressed doubts about the origins of generic medicines, stating that they would like to have some formal assurance of the quality of generics available on the market (and, thereby, showing lack of awareness of, or confidence in, the functions of regulatory authorities).

- If we could be satisfied that the agency who are testing all these drugs, if they could give feedback and reassurance to all GPs that the efficacy and the bioavailability and all of these [generics] were 100% - but I don't think that information is readily available. GP1, male, aged 50-64 years.

- [there are] no guarantees over quality of the [generic] product or over where it's made ... in the developing world, at lower cost, and shipped here, and then sold under branded generics ... you'd want reassurance about quality standards, and you'd want information about where they were manufactured and their licensing laws. GP16, male, aged 40-49 years.
- There doesn’t seem to be the same control of generics, there are so many different
generic companies, and I would feel that there isn’t the same quality control… We
genuinely don’t know where they’re coming from. They say they’re manufactured
in Ireland but the components could be brought in from anywhere. GP31, female,
aged 50-64 years.
Discussion

While there have been numerous publications dealing with generic medicines: their introduction, subsequent use and aspects of acceptance or otherwise; there is relatively limited recent literature regarding the attitudes of physicians towards these products. In this study, we found only seven original papers published between 2003 and 2013 which were focused on GP perspectives [4-10] and, of these, four were not published in English. Usefully, in a comprehensive narrative review, Hassali et al [15] collated international studies published between 1980 and 2008 and coalesced the collective views of physicians as: accepting of generic substitution under policy and economic pressures but having concerns regarding generic drugs’ overall quality, reliability and switchability. This review further theorised that those concerns may prevent full adoption of generic drug prescribing and substitution by physicians, which could lead to escalation in health-care costs for governments, insurers or consumers directly [15].

In the context of the current study, the most recent peer reviewed study of GP attitudes towards generic medicines in Ireland, from 1997 [3], found that 2% of GPs surveyed did not write any prescriptions generically and only 14% of respondents wrote a majority of their prescriptions in this manner. Our study, however, demonstrated that attitudes to generic prescribing have changed in the Irish GP cohort in the intervening time period, with a majority of GPs (88%) stating that they prescribe generics actively, in preference to the originator product. The 1997 study also found that 75% of prescribers were concerned about the reliability and quality of generic drugs. In contrast, our study showed that these opinions have also changed, with over 90% of GPs believing generics to be comparable to the originator medicine in terms of quality and efficacy.

Current concerns of general practitioners appeared to be centred on the potential for stress and confusion that may be caused for patients by the changing aesthetic characteristics of generic preparations, relative to the originator. This, in fact, was held
as a reason for the continued prescription of the originator medicine and could represent a possible stumbling block for successful implementation of the new legislation in Ireland. If “do not substitute” prescriptions for potentially more expensive branded medications are issued for patients who GPs believe may have problems with the differing appearance of generics, this has the potential to negate the intent of the new Act and could significantly reduce the savings which may be reaped from generic substitution and reference pricing.

- *I'd be more inclined to go with the brand name purely so that the patient gets the same thing each time ... For older patients it can cause a lot of confusion when they're getting different brands at different times.* GP11, male, aged 50-64 years.

- *It can be stressful for people adjusting [to different aesthetic presentations], people have the perception that [generics are] different so if somebody's comfortable on the branded product I won’t change them.* GP8, male, aged 40-49 years.

While GP perceptions of generics were primarily positive, this group remain somewhat reluctant to globally adopt generic medicines, as epitomised by the 15% of GPs who expressed a personal preference for taking an originator medication, rather than a generic, if offered a choice.

Approximately 12% of GPs stated that they believed generics might be dangerous compared to the originator, a result that effectively mirrored the views expressed by GPs in previous studies [4, 6, 14]. In contrast with those reports, however, Irish GPs did not necessarily indicate lack of confidence related entirely to the quality of generic medications. Rather, they expressed views regarding the unsuitability of equivalence for generic substitution of some narrow therapeutic index (NTI) drugs, such as some antiepileptic drugs and the fact that excipients may differ between the originator and
equivalent generic formulations (for example: a GP reported a patient having had an allergic reaction to a red dye excipient in a generic product, which was not part of the originator formulation). Indeed, evidence has been published regarding the problematic consequences that arise from differences in excipients used between originator medications and their generic counterparts[16]. Views and experiences expressed in this study showed that a high degree of prescribing is influenced, even mandated, by patient preference or demand.

_Sometimes patients actually ask for a specific, named medicine that they feel that works better than a different medicine they’ve had before... It’s more to do with patient preference that they would think or say that one medicine didn’t suit as well or they didn’t like how it tasted or went down._ GP7, female, aged 30-39 years.

For instance, 94% (32/34) of GPs stated that a patient reported having an issue with a generic medication. Of these, 28 then acceded to their patient’s wishes and prescribed the originator medication in place of the generic. This indicates that, from the point of view of successful implementation of generic substitution and reference pricing, the customer/patient group is a key stakeholder to persuade. Additionally, while patient knowledge of what works best for them is important, there may be a role for GPs in educating/convincing patients to accept generic medicines, and, therefore, supports (such as pamphlets, website etc.) should be made available to GPs to aid them in this. This could be facilitated by use of a novel tool, recently published by our group, based on optimised quality of information and reading ability, for development of websites providing healthcare information [17].

_There’s also pressure put on doctors from patients that the generics aren’t as good as the originator and probably we’re not good enough at explaining to patients that really it’s the same thing._ GP9, male, aged 40-49 years.
Indeed, the anecdote of one GP who reported a patient leaving their practice when their demand for the originator medication was not met, is indicative of the potential issues that could arise if the consumer group is not adequately informed and educated on the topic of generic medicines.

GPs expressed the belief that most negative experiences reported by patients are due to nocebo effects, resulting from patients' negative preconceived notions about generics.

\[ I \text{ would often downplay the significance of issues reported by a patient when taking a generic medication] and suggest to the patient that it had very little to do with the fact that it was a different drug and try to resist, to some extent, the tendency to revert to the originator, but ... if a patient is very adamant about it, it's the lesser of two evils to prescribe the originator brand. The placebo effect is very powerful and can't be discounted. \]

GP24, male, aged 30-39 years.

A question arising from this point, possibly as an area for future research, is whether or not GPs receiving complaints about altered side effects associated with usage of generic drugs are reporting such to the pharmaceutical regulator as adverse events. In fact, research has shown that as many as one in twenty adverse events go unreported [18]. Analogous to the need for education and awareness in the patient group, GPs also stated that (in their opinion) similar interventions are needed for hospital doctors. GPs reported that prescriptions coming from hospitals are almost never written generically. This view is supported by recent research in this area [19]. Thus, there is an opportunity for the Irish health service provider to educate hospital doctors regarding generic medicines. It is worth noting, however, that although the introduction of generic substitution at pharmacy level may negate the financial impacts of non-generic prescribing by hospital doctors, the impact of the perceptions of hospital physicians on patients, regarding generics, cannot be ignored.
As well as education of the general public, GPs expressed the view that they would like to see some assurance of quality of generic medicines from the authorising authority of pharmaceuticals in Ireland: the Irish Medicines Board (IMB).

...there is a lack of information around the standards of generic medication here in Ireland and there exists a patient perception where they feel that they’re getting a cheaper product. GP16, male, aged 40-49 years.

Concerns were expressed regarding origin of medicines, with references made to the growth of pharmaceutical manufacturing, particularly generic products, in countries such as India and China. Those views represent an educational opportunity, implying that at least some GPs are not aware that the IMB applies the same stringent procedures to all medicines approved for the Irish market, regardless of their origins. An analogous need for intervention was documented in the UK, with a 2006 survey showing that 37% of GPs had never heard of the British pharmaceutical regulatory authority [20]. Indeed, the UK situation was referenced to on numerous occasions, being held as an example of what Ireland could achieve, that is, high rates of generic usage with no adverse clinical impact.

Generic prescribing is done at a much higher rate on the NHS, yet are there any greater drug issues, morbidity or mortality, arising there from? There aren’t. I rest my case. GP12, male, aged 50-64 years.

In summary, this paper is only the second published exploration of GP attitudes utilising semi-structured interviews (the first having been done in Melbourne, Australia, using 10 participants [14]), and the first in an Irish context. It is clear from this study, completed in 2013 and accessing over three times as many interviewees, that Irish GPs appear to have a relatively positive view towards generic medicines, albeit tempered with a concern for their patients’ abilities to deal with sometimes confusing changes in medication. Moreover, in an era when usage of generic medicines
is an ever increasing and necessary facet of cost-control in healthcare provision, understanding the root cause of any persisting negative opinions about generics is important in determining any actions be taken to mitigate them.
9. Declarations/Acknowledgements

The design and conducting of this study was approved by the Research Ethics Committee of the Irish College of General Practitioners (ICGP).

The authors declare that they have no conflicts of interest.

This work was supported in part by a scholarship from the Faculty of Education and Health Sciences, University of Limerick, Ireland.

The authors wish to express their sincere thanks to all of the GPs who took part in these interviews.
10. References:

1. **Health (Pricing and Supply of Medical Goods) Act 2013**


20. **Innovating for Health: Patients, physicians, the pharmaceutical industry and the NHS.** In. [http://www.rcplondon.ac.uk/](http://www.rcplondon.ac.uk/); Royal College of Physicians.; 2009.
<table>
<thead>
<tr>
<th>Table 1: Study instrument: semi-structured interview questions</th>
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<tr>
<td>What is your understanding of what a generic medicine is?</td>
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<td>What is your understanding of how a generic medicine differs from an originator medicine?</td>
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<td>What is your understanding of Bioequivalence?</td>
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<td>To the best of your knowledge, what percentage difference is allowed in terms of bioequivalence between an originator medicine and an equivalent generic product?</td>
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<td>What is your understanding of why generic medicines are cheaper than originator medicines?</td>
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<td>What do you believe about how generic medicines compare to brand-name medicines?</td>
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<td>Do you prescribe generic medicines actively?</td>
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<td>Do you ever prescribe generic medicines in preference to originator medicines?</td>
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<td>If yes, please explain why.</td>
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<tr>
<td>Do you ever prescribe originator medicines in preference to generic medicines?</td>
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<td>If yes, please explain why.</td>
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<tr>
<td>What is your opinion as to why use of generic drugs in Ireland has historically been much lower than other European countries?</td>
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<td>Have you ever had a patient report that a generic medicine, which you prescribed for them, didn’t work as effectively as a originator medicine?</td>
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<td>If yes, what type of medicine(s) have you seen this with?</td>
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<td>If yes, can you please give some brief details of what the patient reported having experienced?</td>
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<td>What action did you take in this case?</td>
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<td>Did you then prescribe the originator medicine?</td>
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<td>If yes, was there any reported lack of efficacy from the substituted originator</td>
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<td>medicine?</td>
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<td>Have you ever had a patient report that a originator medicine, which you prescribed for them, didn't work as effectively as a generic medicine?</td>
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<td>If yes, what type of medicine(s) have you seen this with?</td>
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<td>If yes, can you please give some brief details of what the patient reported having experienced?</td>
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<tr>
<td>What action did you take in this case?</td>
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<tr>
<td>Are you aware of the Government’s proposed plans to introduce reference pricing and generic substitution in Ireland?</td>
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<tr>
<td>What is your opinion of this proposed change in Irish legislation?</td>
</tr>
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Table 2 – Study instrument: structured questions and GP responses

| Do you strongly agree, agree, neither agree nor disagree, disagree, strongly disagree with the following statements: | n=34 |
|---|---|---|---|---|
| | SA/A\(^1\) | SD/D\(^2\) | N\(^3\) |
| | n | % | n | % | n | % |
| Generic medicines are generally of the same quality as originator medicines. | 31 | 91.2 | 3 | 8.8 | 0 | 0.0 |
| Generic medicines are generally poorer quality than originator medicines. | 3 | 8.8 | 30 | 88.2 | 1 | 2.9 |
| Generic medicines are generally better quality than originator medicines. | 0 | 0.0 | 25 | 73.5 | 9 | 26.5 |
| Generic medicines work as effectively as originator medicines. | 31 | 91.2 | 2 | 5.9 | 1 | 2.9 |
| Generic meds work better than originator meds. | 0 | 0.0 | 31 | 91.2 | 3 | 8.8 |
| Generic meds don’t work as well as originator meds | 4 | 11.8 | 27 | 79.4 | 3 | 8.8 |
| Generic medicines may be dangerous compared to originator meds | 4 | 11.8 | 29 | 85.3 | 1 | 2.9 |
| Generic Meds are as safe as originator meds. | 30 | 88.2 | 2 | 5.9 | 2 | 5.9 |
| Generic medicines are manufactured to the same quality as originator medicines. | 24 | 70.6 | 5 | 14.7 | 5 | 14.7 |
| Generic meds are manufactured to a poorer quality than originator meds | 4 | 11.8 | 25 | 73.5 | 5 | 14.7 |
| Generic meds are manufactured to a higher quality than originator meds | 0 | 0.0 | 28 | 82.4 | 6 | 17.6 |
| Generic meds are cheaper to buy than | 30 | 88.2 | 2 | 5.9 | 2 | 5.9 |
originator meds.

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<th>1</th>
<th>2.9</th>
<th>32</th>
<th>94.1</th>
<th>1</th>
<th>2.9</th>
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<tbody>
<tr>
<td>Generic meds are cheaper because they are of inferior quality to originator meds.</td>
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</tr>
<tr>
<td>If I were ill, I would be happy to take a generic med if my doctor prescribed it for me.</td>
<td>32</td>
<td>94.1</td>
<td>1</td>
<td>2.9</td>
<td>1</td>
<td>2.9</td>
</tr>
<tr>
<td>If I were ill, I would prefer to take an originator med rather than a generic med, even if it is more expensive.</td>
<td>5</td>
<td>14.7</td>
<td>23</td>
<td>67.6</td>
<td>6</td>
<td>17.6</td>
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1Strongly Agree/Agree

2Strongly disagree/Disagree

3Neutral/No opinion
Chapter 6

Perceptions and attitudes of community pharmacists regarding generic medicines: a mixed methods study.

Published in *Journal of Managed Care & Speciality Pharmacy*.  

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Perceptions and attitudes of community pharmacists regarding generic medicines.

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Abstract

Introduction

Following the enactment of legislation in June 2013, and to benefit from associated cost-savings, generic substitution and reference pricing of medicines has been introduced, for the first time, in Ireland. With attitudes and behaviours of healthcare professionals being key to the successful implementation of this policy, we sought to determine the perceptions towards generic medicines amongst community pharmacists.

Methodology

One-to-one semi-structured interviews were performed with 44 community pharmacists recruited from Ireland’s Midwest, South and Southwest regions. Interviews were transcribed and analysed using NVivo (version 9).

Results

97.7% of pharmacists believed that generics were of a similar quality to, and 95.5% stated that they were as effective as, the originator. However, a small number demonstrated some reticence regarding generics: 9.1% believed that generics were not manufactured to the same quality as the originator, 6.8% stated they would prefer to take an originator medicine themselves and 6.8% reported having experienced quality issues with generic medicines. 88.6% of pharmacists reported receiving patient complaints regarding use of generic medicine, although 63.6% suggested that this was due to a nocebo effect as a result of patients’ preconceived notions that generics were inferior. Only a minority (20.5%) reported that they had attempted to educate patients as to the equivalency of generics. Although 79.5% were in favour of Ireland’s new legislation relating to generic medicines, 45.5% expressed concerns regarding its practical implementation.

Discussion

This is the first study of community pharmacists’ attitudes towards generic medicines in Ireland. Conducted uniquely in the time period just prior to the implementation of
legislation intended to increase usage of generics, this study highlights that this key stakeholder group had positive attitudes towards generics and the legislation that will promote their use. Concerns regarding patient perception and experience, clinical effectiveness and manufacturing quality were identified and interventions supporting the implementation of the new legislation would benefit from these concerns being addressed.

**Keywords**

Community pharmacists; generic drugs; professional education; patient education; health policy, Ireland.
Introduction

The Irish Government has recently (June 2013) [1] signed a new Act into law, (the Health (Pricing and Supply of Medical Goods) Act 2013) [2], which will introduce the legal basis for generic substitution and reference pricing for the first time. As a consequence of this new legislation, patients in Ireland are now more likely than ever before to receive a generic medicine. Thus, pharmacists’ opinions of, and attitudes towards, generic medicines are critical to the success of the changes being implemented. Attitudes of pharmacists in Ireland towards generics have not been studied in the past. In fact, to the authors’ knowledge, this topic has not been described in, or been the focus of, any peer-reviewed published research. While assessments of pharmacist perceptions of generic medicines have been carried out in a limited number of other countries, in the past 10 years: New Zealand [3], Portugal [4], South Africa [5], Malaysia [6], France [7] and Sweden [8] – and also in relation to specific medications such as antiepileptic formulations [9] and inhalers [10] - a PubMed search (June 2013) did not return any peer-reviewed publications on the topic of pharmacist perceptions of generic medicines in Ireland. In fact, as the eight studies referenced above were the only published investigations on the topic of pharmacist perception of generic medicines (in the last 10 years) – this appears to be a relatively underexplored area, internationally.

With Ireland on the cusp of a major modification in healthcare practices, there are many potential hurdles to be overcome during the introduction of such changes [11]. As the attitudes and behaviours of healthcare professionals, towards generic medicines, are pivotal to the successful implementation of the new Act, the objective of this novel study was to assess these perceptions, amongst community pharmacists in Ireland, in the time leading up to the enactment of the new legislation; and to determine what challenges might arise as a consequence of the opinions of this stakeholder group.
Methodology

Preparation of study instrument

The study instrument was informed by a recently published review of the usage of generic medicines and how policy changes to promote the use of generic medicines may affect healthcare provision [12]; and by the personal experience of the primary author and study designer (who has over 15 years of quality management and regulatory affairs within the pharmaceutical and biopharmaceutical industry).

Questions for semi-structured interview were prepared and subjected to cognitive testing, the aim of which was to ensure the test questions were understood as intended. The intent of the interviews was to elucidate perceptions relating to general opinion & understanding of generic medicines, behaviours towards generic medicines (e.g., prescribing behaviours in the case of GPs and dispensing behaviours in the case of community pharmacists), opinions as to the historical poor usage of generics in Ireland, beliefs held as to the quality and efficacy of generics and how these compare to proprietary (that is, brand-name) medicines and knowledge & opinion of the impending legislative change.

Cognitive testing was performed with three individuals in each cohort group who were firstly asked the question, then allowed to provide a response and after responding were asked what their understanding of the question was. Amendments were made to questions based on responses from all three test participants. The responses of these participants to the interview questions were not included in those finally analysed for this study. The interviews used in the study began after cognitive testing had been completed and the interview questions had been suitably amended.
Recruitment and survey interviews

Pharmacists were approached in person, while in the pharmacy, and invited to participate in the study. A verbal explanation of the study was provided, and an invitation letter was offered. One-to-one interviews were carried out with consenting pharmacists between June and October 2012, some face to face and others via telephone. Interviews, which were recorded (with the interviewee’s consent), were semi-structured and based on a series of questions (see Table 1) to which open, or qualitative, answers could be given. Additional supporting assessment of opinions was completed using a series of structured questions to which participants could select from predefined answers (Table 3). In this instance, a five-point Likert scale [13] was used with a single response allowed for each question, selected from: Strongly Agree, Agree, Neutral, Disagree and Strongly Disagree and participants were also free to volunteer additional commentary on each question. Furthermore, participants were offered the opportunity to freely express any additional opinions or views at the end of the interview session. Interviews were conducted until data saturation had been achieved.

Approval of the design and conducting of this study was granted by the Research Ethics Committee of the Irish College of General Practitioners (ICGP).

Analysis of data

Using a grounded theory approach [14], interviews were transcribed, verbatim, and imported into NVivo (version 9) for analysis. Using an inductive process, transcripts were open coded for themes relating to interviewee opinions, perceptions and behaviours, including any other emerging themes, and the results were analysed using NVivo. To facilitate visualisation and understanding of the numbers of participants holding the perceptions/behaviours that were coded into specific themes, these were expressed as a percentage of the total number of participants. Interviews were
conducted until saturation of data was observed. Analysis was completed by the primary researcher (SD) and reviewed to ensure reliability and rigor of the analysis by a senior investigator (CD).
Results

Pharmacist interviews analysis

Forty-four (44) community pharmacists were interviewed. Demographics of the group are available in table 2. Participating pharmacists were located in counties Limerick, Tipperary, Cork and Waterford.

Opinions regarding quality, efficacy and safety of generics (Table 3).

The majority of pharmacists (97.7%) were of the belief that generic medicines are of the same quality as the originator, with 95.5% holding the view that they work as effectively. All of the pharmacists interviewed believed that generics are as safe as the originator. A small number (9.1%) however, were of the opinion that generics are not manufactured to the same quality as originator medicines, and were of the view that generic manufacturing is of a poorer standard.

93.2% of pharmacists stated that they would take a generic medicine themselves, with a small number (6.8%) stating that they would prefer to take the originator, rather than an equivalent generic, if offered a choice.

Some quotations on the theme of the comparability of generic and originator medicines include:

- To be honest … for any decisions that I make, or anything I say to customers, if it was me or any of my family and I was given the option of a generic medicine I would go for it, I would absolutely take it. Female, aged 30-39 years.

- I believe that they are equivalent in therapeutic value and I would have no hesitation in recommending a generic product over a branded one to a customer. Male, aged 19-29 years.
- I think generic medications are brilliant to be honest with you the only downside is people's perceptions, they think that the brands are better when in reality generics are just as good. Male, aged 18-29 years.

Pharmacist experiences with patient complaints regarding generic medicines

88.6% (39/44) of pharmacists reported receiving patient complaints associated with use of a generic medicine. (Interestingly, of the five who had not experienced this, one pharmacist stated that they did not deal with generics). Pharmacists reported that when a patient had an issue with a generic, the main experiences described were that it was not as effective, or that they experienced altered or increased side effects. 63.6% (28/44) of pharmacists expressed an opinion that at least some of the negative experiences reported by patients were not actual, but rather caused by nocebo effect, (that is, that patients’ pre-conceived ideas as to a perceived sub-standard nature of generics led to them having a negative experience with the generic), rather an actual issue with the medication.

Quotations relating to the theme of negative patient perception include:

- On paper they should be the same and should act in the same way, but we have had cases where people have come in and said that they didn’t find a generic as effective as the original and they prefer the original ... and from customers’ queries, some of them don’t find that they’re the same. Female, aged 30-39 years.
... [generic medicines] work the same therapeutically but I suppose people just have this notion that if it’s cheaper it can’t be as good, that’s the patients perception of it I think. Female, aged 30-39 years.
- I think, to be honest, any time [a patient has] had a problem with a generic instead of a brand is because they feel that they’re being cheated, they basically
feel that they’re getting second best because it’s cheaper ... Female, aged 30-39 years.

Medication types most reported as being problematic included: PPIs (27.3% - 12/44), statins (18.2% - 8/44), inhalers (6.8% - 3/44), antihypertensives (6.8% - 3/44), antibiotics (6.8% - 3/44), antidepressants (4.5% - 2/44), and analgesics (2.3% - 1/44).

Conversely, 25% (11/44) of pharmacists stated that a patient had reported an issue with an originator medicine compared to a generic. In most cases, as the patient had received the generic before the originator medication, pharmacists indicated that, in their opinion, the patient’s preference is often for the medicine they first encounter and that such issues are more likely to be due to a change having occurred, rather than an actual issue with the medicine per se.

I think if [the patient] started on a generic, and it’s what they know, they prefer that; so I think that it’s maybe the change - it’s a change management issue more than anything else. Male, aged 40-49 years.

In the situation where they received a complaint from a patient related to use of a generic medicine, and the patient requested the originator instead, 77.3% (34/44) of pharmacists stated that they would accede to the patient’s preferences.

...one woman I can’t convince that the generic coated aspirin would not have caused her to bleed, it’s totally in her mind, you can’t win those battles. Male, aged 50-64 years.

... [if] you know what a patient is satisfied with, you generally won’t rock their boat. Female, aged over 65 years.

Only 20.5% (9/44) stated they would attempt to educate the patient.

... the first thing I would do is I’d try and explain the situation but ... at the end of the day I think quite often with people who are coming in, they’ve made up
their mind and there’s really very little you can do at that stage. Male, aged 30-39 years.

- You try to explain to them that it is exactly the same medication and explain to them that it’s the same amount of drug just called something else, that 500 milligrams of the generic drug is exactly the same, that it’s made in the same way, but then if they’re still going “no, no, no”, we’d give them the original.

Female, aged 30-39 years.

When asked about the differences between an originator and an equivalent generic, a small number of pharmacists (4.5% - 2/44) expressed an opinion that there was no difference. Given that the only requirement for similarity (in terms of ingredients) between an originator product and a generic equivalent is that the same active ingredient be used (excipients, thus, may vary) and that generic products are often aesthetically different to the originator – this could be a source of confusion for patients, if the differences in appearance and excipient content are not adequately explained to them.

Opinions regarding low historic usage of generics

When asked what their opinion was as to why usage of generics in Ireland has been low in the past, the main reasons given by pharmacists were: Lack of generic prescribing (31.4% - 27/44) (the primary reasons given for this were familiarity with trade names on the part of prescribers and their lack of knowledge of the generic names of medicines); Lack of government incentive or pressure for generics usage (50% - 22/44); the influence of the pharmaceutical industry (that is, proprietary manufacturers) in Ireland (40.9% - 18/44); poor understanding of generics by consumers (40.9% - 18/44); brand consciousness or loyalty on the part of the consumer (including an element of patients
being used to a particular brand and having poor cost consciousness) (38.6% - 17/44); and the non-allowance of generic substitution (31.8% - 14/44).

**Pharmacist perceptions of quality and patient issues with generic medicines**

A minority of pharmacists (6.8% - 3/44) reported having experienced quality issues with generic medicines. Issues reported included crumbling tablets and having difficulty getting tablets out of blister packs. The pharmacists reported that, in their opinion, these issues have effects on consumer confidence in generic products.

- There have been an increasing number of incidences where people have come back and said that the quality of the solid dosage form is significantly poorer and there is one company who are particularly culpable in this regard, whereby their tablets crumble on punching from a blister pack. Their capsules are virtually impossible to get out of the blister pack. Now that’s not to say that there’s anything wrong with the actual raw ingredient, with the medication within the solid dosage form, but there are significant shortcomings in the way those solid dosage forms are compounded. And I think that that, if it’s not rectified, is going to compromise patients’ attitudes towards generic medicines. Male, aged 40-49 years.

- I’ve had a couple of issues with a few [generic] tables - they have disintegrated, over time, and that problem didn’t arise with the original drug.... but 99% of the time there’s no issue with the quality of [generics]. Female, aged 30-39 years.

Poorer packaging was also mentioned as being perceived as a negative (9.1% - 4/44), and one pharmacist stated, anecdotally, that differences between originator and generic packaging can even cause issues for patients (e.g., where an originator brand tablet had the days of the week printed on the foil, serving as a reminder to the patient as to
whether that day’s medication had been taken or not, but similar printing was not available with the generics). This led to patient preference for the originator medicine.

…packaging-wise you definitely notice a difference with some of the generics, that you wouldn’t have half as much detail on the packaging, the boxes are quite plain. I know some customers will only take [the originator] tablets that actually have the label Monday, Tuesday, Wednesday at the back of them and a lot of generics won’t have any of that detail on the [foil]. Female, aged 30-39 years.

- I’d like the generic companies to package their stuff better, if it’s packaged shabbily it gives a bad impression. Now I know it’s nothing to do with the effectivity of the substance but some of them are very poorly packaged. Male, aged over 65 years.

Pharmacists also reported the opinion that patients are sometimes resistant to change (43.2% - 19/44) and that the different aesthetic presentation of generics can cause problems of confusion and medication errors for some, particularly elderly, patients.

…my grandmother in law … was on a generic simvastatin which was changed to another simvastatin which happened to be the same colour and shape, with no markings, as her blood pressure tablet and she ended up taking double blood pressure tablets for about 2 weeks. Male, aged 30-39 years.

- If the demographic of patients you deal with are elderly people and you know they just don’t like change, they want to stay the same, so you’re kind of on the back foot immediately if you’re trying a new drug. Male, aged 30-39 years.

As a consequence, education of patients was seen as a necessary step for wider acceptance of generics, and 34.1% (15/44) of pharmacists stated that, in their opinion, patients see generics as being a sub-standard or lesser alternative, due to the fact that they are cheaper, described as: “own-brand syndrome”. Indeed, pharmacists expressed
the opinion that patients in Ireland hold a significant preference for branded medications (36.4% - 16/44).

Quotation from a non-Irish pharmacist: *my experience with the Irish psyche is that they're very brand oriented, I don’t know why, but they tend to be very brand oriented. And I think that could be impacting on why they don’t like generics, they like the original brand … but as soon as you tell them it’s a copy, it’s a generic, they will think it’s a second class drug.* Male, aged 40-49 years.

- *I just think people are very used to getting brands, they think all brands are better. It can be to do with the prescribers; some doctors prescribe a brand because that’s what they’ve always known.* Male, aged 18-29 years.

A small number of pharmacists (11.4% - 5/44) reported patients asking for cheaper generics, however, this was in a minority of cases and tended to be limited to private patients, who, in the views of the pharmacists, have a better understanding and education regarding generics. Pharmacists additionally made reference to GMS (General Medical Services) patients getting more branded medication than private [i.e., self-paying] patients. (For clarity: In Ireland, the General Medical Services (GMS or medical card), scheme is available to persons who are unable, without undue financial hardship, to arrange general practitioner medical and surgical services for themselves and their dependents, and all persons aged 70 years and over. Being in receipt of a medical card allows the holder to receive a free (or subsidised) general medical service).

- *I think that private patients, paying themselves, don’t mind, but that the people that don’t have to pay are the ones that want to stick to the original brand…. it’s GMS patients that have a problem with it, not the private patients.* Female, aged 30-39 years.

- *I think an awful lot of people have it in their head, that the generic isn’t as good. As well, medical card patients have commented a few times, ‘it’s because I’m on a*
medical card that you’re giving me the cheaper tablet’. That’s the kind of presumption I think that’s out there - people think that because it's cheaper, they don’t see generic as equivalent, but as a lesser tablet. Female, aged 30-39 years.

Furthermore, some pharmacists were of the opinion that branding of generics should be disallowed, as it is contrary to the intent of having generic medication, and resulted issues for them with regard to having to stock multiple “brands” of the same generic medication.

Get rid of branded generics…either it’s a generic or its not; there’s no need for the middle ground of a branded generic. Female, aged 30-39 years.
Opinions regarding new legislation

All of the pharmacists interviewed were aware of the Irish government’s proposed plans to introduce reference pricing and generic substitution in Ireland. When asked about their opinions towards the new legislation, a majority of pharmacists – 79.5% (35/44) - indicated that they were positive or accepting of it. A number of pharmacists, 54.5% (24/44), were of the opinion that it made financial sense and is necessary for the country, although many pharmacists – 45.5% (20/44) - expressed concerns and reported that they anticipated having issues with its practical implementation.

- Bring it on, pharmacists have been waiting for it for years, we have absolutely no problem, we’re here ready to go, just give us the guidelines and let us just work on it. I’m all about value, we have to be, as professionals and as people that are actually concerned about people’s health and their finances, we want to give the best value, we’re not in the business of trying to rip people off, so give us that law so we can do what we’re supposed to do which is look after our customers in every way possible and make them feel better. Female, aged 30-39 years.
- I can envisage that people will have issues, because we’ve had issues before with people and when it does come to it, I’d say there is a certain percentage of the population that won’t be happy with taking the generic one or whatever one is the best price at the time, because they’re just comfortable taking their one particular brand and that’s it. Female, aged 30-39 years.
Discussion

Perceptions of pharmacists’ in Ireland towards generic medicines have not been studied in the past (a PubMed search for publications about the opinions of pharmacists in Ireland towards generic medicines, done in June 2013, found no (zero) results).

Internationally, a limited number of assessments have taken place in countries such as New Zealand [3], Portugal [4], South Africa [5], Malaysia [6], France [7], and Sweden [8]; including studies on views held regarding specific medication types, such as antiepileptic drugs (AEDs) [9] and inhalers [10]. Given the major changes currently underway in the Irish healthcare system (that is, the introduction for the first time of reference pricing and generic substitution), the opinions and behaviours of this critical stakeholder group have the potential to be pivotal to the success or failure of the changes being implemented.

In contrast to other reports of reticent views of pharmacists [3, 6, 10], this study has shown that pharmacists in Ireland were generally positive towards, and accepting of, generic medicines; holding the view that they are as effective as the originator (excepting non-substitutable situations, such as with NTI drugs, and that differences in presentation can be a source of problems for some patients). Very few pharmacists expressed reticent opinions and one of the primary concerns, as has been reported elsewhere [8], was that confusion caused, due to differing aesthetic presentations of generic medicines, has the potential to be problematic for patients.

While a majority of pharmacists were in favour of the new legislation, (with references made to the UK situation: that no clinical issues linked to a much greater use of generic medicines are seen, thus the same situation could reasonably be expected in Ireland without risk to patients) about half of the pharmacists interviewed (45.5% - 20/44) expressed concerns as to the practical implementation of associated changes. Concerns included the impact on the running of the pharmacy as well as on patients.
Pharmacists were of the view that they could meet considerable resistance from patients and that they, being at the “coal face”, may need to spend substantial periods of time explaining the new system to patients, if adequate educative interventions are not put in place by either the government or other interested bodies (e.g., the Pharmaceutical Society of Ireland). Indeed, the requirement for education of the general public, to improve opinions and, therefore, increase patient acceptance of generics, was a recurring theme in this study, as it has been in other studies [4, 5, 7, 8]. Increased public awareness and education were considered to be fundamental to improved acceptance of generics by consumers. In fact, an anecdote told by one pharmacist, regarding how she convinced a patient, who was reticent to take a generic version of an inhaler, is indicative of how such an intervention might work. The pharmacist told how she brought out both the generic and the proprietary inhalers and showed both to the patient, pointing out the ingredients of both and showing the patient that they were the same. This practical and clever demonstration of equivalence convinced the patient to try the generic inhaler, and the pharmacist indicated that they did not return with any subsequent issues. Such examples should be made use of when designing educational interventions for patients.

Patient preference was seen to have a considerable influence on dispensing practices, with many pharmacists (77.3% - 34/44) acceding to patients’ wishes for brand-name medications. This, despite the fact that pharmacists believed that the majority of issues/complaints from patients regarding generics are not actual, but rather are as a result of a nocebo effect - due to the patients’ prejudices regarding generic medicines.

*I’ve had some cases [of patient complaints] where it’s actually say, the Pfizer atorvastatin generic, comes off the same line as Lipitor, the only thing you can blame is patient perception when it’s exactly the same thing. Even after I told [the
Pharmacists were of the opinion that this negative patient perception may be based on the fact that generics are less expensive, and, therefore, in the patients’ opinion, cannot be as good, leading to a so-called “own-brand syndrome”.

*I think maybe a lot of the time “generic” and “cheaper” are put in the same sentence, so people think because it’s cheaper it can’t be as good as the original.*

Also, pharmacists believed that many negative patient experiences were due to changes in medication and that the first medication that the patient is exposed to will tend to be their preferred option. Therefore, when this is changed, the patient is more likely to experience a problem.

*I did have one particular incident where [a patient] reported [a problem with a generic] and [the medication] was actually exactly the same thing, it was a parallel import as opposed to a generic - they saw the pack was different, and they said [the medicine] didn’t work the same, they didn’t want that one - but it was, in every sense, exactly the same medication.*

Additionally, there may be a part to play for generics manufacturers/licence holders in improving the opinions of consumers regarding their products. One aspect could be to ensure that their packaging is of a standard at least equivalent to that of the originator and, where relevant, to ensure that it provides the same facilities for prompting/reminding of patients to take their medication (e.g., the anecdote where a pharmacist stated that continued use of one proprietary brand was due to patient preference for the packaging, as the days of the week were printed on the blister pack foil). There may also be an argument for regulators approving generic medicines to require that if patient aids are part of the originator packaging, any generic equivalents
must provide similar aids in order to obtain a marketing authorisation. Moreover, a theme emerged on the topic of branded generics: while generic substitution makes the issue of pharmacists needing stocks of multiple branded generics moot, (that is, unless a “do not substitute” prescription has been written), pharmacists expressed views that branding of generics should not be permitted as, practical aspects aside, branding of generic medications is not in keeping with the intention of provision of generic medicines. Indeed, a recent report from the Irish Economic and Social Research Institute (ESRI) on the costing of generics in Ireland has shown them to be similar to the original branded medication, thereby not resulting in substantial benefit to either the Irish exchequer or consumer [15].

As improved consumer confidence in generics was considered to be one of the major hurdles to be overcome in improving use of generics in Ireland, (similarly noted in other studies [4, 5, 8]), the question was posed by pharmacists: how can this information/education be provided in a manner that is easy for patients to access and understand? While one pharmacist provided an anecdote about cleverly showing a patient both the originator and generic products (asthma inhalers in this case), side-by-side to prove their equivalency, the practicality of doing this on a day-to-day, patient-to-patient basis is obviously something that busy pharmacists cannot undertake.

…it would make our job a lot easier when you have to say to someone “you can’t have [the originator] brand anymore because the government is only going to pay for [the generic] one, if you want [the originator] you have to pay the difference between the price”, to have a bit of backup from the State on that would be good. Male, aged 30-39 years.

Provision of such educational supports could be facilitated, for example, by use of a novel tool, recently published by our group, based on optimised quality of information and reading ability, for development of websites providing healthcare information [16].
The resulting availability of easy to read hand-outs/pamphlets, websites, or similar sources of information, may not only provide consumers with the information they need to dispel myths about generics and, hence, improve their confidence but may also have the dual effect of making the role of the pharmacist easier during a time of upheaval and change.

A possible limitation of this study could be in the area of selection of participants; all of the pharmacists interviewed were community pharmacists, whose opinions may differ from pharmacists working in hospital, or other, settings. Furthermore, differing interview settings (some participants were interviewed face-to-face, and others were interviewed over the telephone) might have influenced the data gathered in this study [17]. However, review and comparison of the themes emerging from participants interviewed in different settings did not show any substantial difference in the opinions, perceptions and behaviours expressed between participants. Moreover, while the authors acknowledge that quantification of qualitative data is sometimes contentious, we chose to adopt this approach in order to best provide easy visualisation of results and offer a more comprehensive insight into the patient perspective. The strengths of such an approach have been discussed by Schonfelder in 2011 [18].

A strength of this study in the number of subjects used for qualitative interview; the number of participants in this study compared favourably with the only other semi-structured interview-based studies that could be found in PubMed (i.e., 16 participants were interviewed for an analogous study in Sweden [8] and six pharmacists (from a total of fifteen healthcare professionals) were interviewed for a similar study in South Africa [5]).
Conclusion

Community pharmacists in Ireland hold positive opinions about usage of generic medicines however they have concerns about the practical implementation of reference pricing and generic substitution. Concerns were also raised about the impact on patients of the varying appearance of generic medicines and regarding the lack of confidence that they observe in the general public in relation to usage of generic medicines.
Acknowledgements

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The authors wish to express their sincere thanks to all of the pharmacists who took part in these interviews.
Table 1 – Study Instrument: Questions that formed the basis for semi-structured interviews

<table>
<thead>
<tr>
<th>Question</th>
<th>Additional Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>What is your understanding of what a generic medicine is?</td>
<td></td>
</tr>
<tr>
<td>What is your understanding of how a generic medicine differs from an originator medicine?</td>
<td></td>
</tr>
<tr>
<td>What is your understanding of Bioequivalence?</td>
<td></td>
</tr>
<tr>
<td>To the best of your knowledge, what percentage difference is allowed in terms of bioequivalence between an originator medicine and an equivalent generic product?</td>
<td></td>
</tr>
<tr>
<td>What is your understanding of why generic medicines are cheaper than originator medicines?</td>
<td></td>
</tr>
<tr>
<td>What do you believe about how generic medicines compare to brand-name medicines?</td>
<td></td>
</tr>
<tr>
<td>What is your opinion as to why use of generic drugs in Ireland has historically been much lower than other European countries?</td>
<td></td>
</tr>
<tr>
<td>Have you ever had a patient report that a generic medicine, which you dispensed for them, did not work as effectively as an originator medicine?</td>
<td></td>
</tr>
<tr>
<td>If yes, what type of medicine(s) have you seen this with?</td>
<td></td>
</tr>
<tr>
<td>Can you please give some brief details of what the patient reported having experienced?</td>
<td></td>
</tr>
<tr>
<td>What action did you take in this case?</td>
<td></td>
</tr>
<tr>
<td>Did you then dispense the originator medicine?</td>
<td></td>
</tr>
<tr>
<td>If yes, was there any reported lack of efficacy from the substituted originator medicine?</td>
<td></td>
</tr>
<tr>
<td>Have you ever had a patient report that an originator medicine, which you dispensed for them, did not work as effectively as a generic medicine?</td>
<td></td>
</tr>
<tr>
<td>If yes, what type of medicine(s) have you seen this with?</td>
<td></td>
</tr>
<tr>
<td>Can you please give some brief details of what the patient reported having experienced?</td>
<td></td>
</tr>
<tr>
<td>What action did you take in this case?</td>
<td></td>
</tr>
<tr>
<td>Are you aware of the government’s plans to introduce reference pricing and generic substitution in Ireland?</td>
<td></td>
</tr>
<tr>
<td>What is your opinion of this proposed change in Irish legislation?</td>
<td></td>
</tr>
</tbody>
</table>
Table 2 – Demographics

<table>
<thead>
<tr>
<th>Group</th>
<th>Gender</th>
<th>AGE 18-29</th>
<th>AGE 30-39</th>
<th>AGE 40-49</th>
<th>AGE 50-64</th>
<th>AGE 65+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharmacists</td>
<td>M</td>
<td>23</td>
<td>9</td>
<td>17</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>n=44</td>
<td>F</td>
<td>21</td>
<td>17</td>
<td>10</td>
<td>5</td>
<td>3</td>
</tr>
</tbody>
</table>
Table 3 – Study Instrument: Supporting structured questions and pharmacist responses

<table>
<thead>
<tr>
<th>Statement</th>
<th>Pharmacists n=44</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SA/A(^1)</td>
</tr>
<tr>
<td></td>
<td>n</td>
</tr>
<tr>
<td>Generic medicines are generally of the same quality as originator medicines.</td>
<td>43</td>
</tr>
<tr>
<td>Generic medicines are generally poorer quality than originator medicines.</td>
<td>1</td>
</tr>
<tr>
<td>Generic medicines are generally better quality than originator medicines.</td>
<td>1</td>
</tr>
<tr>
<td>Generic medicines work as effectively as originator medicines.</td>
<td>42</td>
</tr>
<tr>
<td>Generic medicines work better than originator medicines.</td>
<td>0</td>
</tr>
<tr>
<td>Generic medicines don't work as well as originator medicines</td>
<td>1</td>
</tr>
<tr>
<td>Generic medicines may be dangerous compared to originator medicines</td>
<td>2</td>
</tr>
<tr>
<td>Generic Medicines are as safe as originator medicines.</td>
<td>44</td>
</tr>
<tr>
<td>Generic medicines are manufactured to the same quality as originator medicines.</td>
<td>35</td>
</tr>
<tr>
<td>Generic medicines are manufactured to a poorer quality than originator medicines.</td>
<td>4</td>
</tr>
<tr>
<td>Generic medicines are manufactured to a higher quality than originator medicines.</td>
<td>0</td>
</tr>
<tr>
<td>Generic medicines are cheaper to buy than originator medicines.</td>
<td>41</td>
</tr>
<tr>
<td>Generic medicines are cheaper because they are of inferior quality to originator medicines.</td>
<td>1</td>
</tr>
<tr>
<td>If I were ill, I would be happy to take a generic medicine if my doctor prescribed it for me.</td>
<td>41</td>
</tr>
<tr>
<td>If I were ill, I would prefer to take an originator medicine rather than a generic medicine, even if it is more expensive.</td>
<td>3</td>
</tr>
</tbody>
</table>

\(^1\)Strongly Agree/Agree

\(^2\)Strongly disagree/Disagree

\(^3\)Neutral/No opinion
References:


9. McAuley JW, Chen AY, Elliott JO, Shneker BF: An assessment of patient and pharmacist knowledge of and attitudes toward reporting adverse
drug events due to formulation switching in patients with epilepsy.


11. Proposed Model for Reference Pricing and Generic Substitution


Chapter 7

Patient perceptions of generic medicines: a mixed-methods study.

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Title
Patient perceptions of generic medicines: a mixed-methods study.

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Abstract

Introduction

In an attempt to benefit from the cost-savings associated with use of generic medicines, in June 2013 Ireland introduced generic substitution and reference pricing for the first time. Perceptions of Irish patients towards generic medicines, however, have not been published previously. Therefore, the objective of this study was to assess how generic medicines were perceived amongst patients in the time leading up to the enactment of the new legislation.

Methodology

Forty-two patients were recruited from general practices affiliated with the Graduate Entry Medical School at the University of Limerick and from community pharmacies. Interviews were semi-structured and included quantitative assessments of opinions using fifteen structured questions and a five-point Likert scale response system. Interview transcripts were coded and thematically analysed using NVivo (version 9), for qualitative data. Quantitative data were analysed using SPSS (version 20).

Results

Nearly a third (31%) of patients had no knowledge of generic medicines and 38.5% of those exhibited confusion between the words “generic” and “genetic”. Almost a quarter (24%) held the view that generics were of poorer quality than originators while 18% expressed the opinion that generics do not work as well as originator products. Approximately a third (30%) of patients believed that generics were manufactured to a poorer quality with 29% holding the view that generics are less expensive due to being of inferior quality. Nearly 90% of patients stated they would take a generic medicine if it were prescribed by their GP, however, 24% of patients stated a preference, if offered a choice, for the originator medication. Additionally, a majority of patients (86%) were in favour of reference pricing and generic substitution. 50% of the patients interviewed
stated that a leaflet, or similar, with appropriate, understandable and accessible information regarding generic medicines would be of use to them.

**Conclusion**

This is the first study of patients’ attitudes towards generic medicines in Ireland. Conducted in the time period leading up to the implementation of legislation introducing generic substitution and reference pricing, it highlights variable knowledge about generic medicines among this key stakeholder group. Although patients are supportive of their more widespread use, concerns regarding safety, clinical effectiveness and manufacturing quality of generic medicines were identified.
Key Points For Decision Makers

1. Up to June 2013 Ireland did not have a system of generic substitution or reference pricing, as is the norm in many other countries. As such, pharmacists in Ireland were legally obliged to dispense medicines exactly as written on the prescription and could not dispense a lower cost, equivalent generic alternative if the proprietary medicine had been prescribed by name. Hence the state incurred the full cost of such medicines for those on state funded medicines schemes.

2. Spending on pharmaceuticals in Ireland is high, the highest in the EU per capita in 2010 [1], for example: the annual cost of medicines under the state funded drugs schemes increased from €564m in 2000 to €1,961m in 2009 [2]. Thus, the Irish government has recognized that increasing usage of generic medicines has the potential to make significant savings to the exchequer. As such, new legislation introducing generic substitution and reference pricing in Ireland was signed into law in June 2013.

3. No studies have been published in the past that investigated perceptions of generic medicines in the Irish patient cohort.

4. Patients are not fully aware of what generic medicines are and express doubts as to their efficacy and quality. Despite these misgivings, patients exhibit a high degree of trust in medical professionals and would take a generic drug, if prescribed by a trusted physician, despite their own lack of confidence in generics.
Introduction

In June 2013, the Irish Government signed a new Act into law (the Health (Pricing and Supply of Medical Goods) Act 2013) [3]. Despite generic substitution\(^1\) and reference pricing\(^2\) being used in other European countries [4] (for example, generic substitution was introduced in Sweden in 2002 [5], in Finland in 2003 [6] and has long been an integral part of the British National Health System, amongst others [7]), the situation in Ireland, prior to this legislation, required that the pharmacist supply only the medicine indicated by the prescribing physician, even if there was a less expensive, generic version available (unless the prescription was written generically, that is, using the non-proprietary name of the medicine). The implication of this legislation is that generic substitution and reference pricing will be implemented for the first time in this market. A practical aspect of this implementation, targeting reduction of Ireland’s considerable drug expenditure costs (in 2010, per capita spending on pharmaceuticals in Ireland was the highest in the EU, 34% above the average [1]), is that Irish patients are now more likely than ever before to receive a generic medicine. Consequently, patients’ perceptions of generic medicines will be an important facet for successful implementation of the new Act. Despite this, to the authors’ knowledge, as of July 2013, no research on Irish patients’ views had been published. Hence, there is a gap in knowledge related to Irish patients’ perceptions of generic medicines. Furthermore, only eighteen reports (five of which were not in English) have been published, in the last ten

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\(^1\) Generic substitution is the substitution of an equivalent, non-branded, medicine for a prescribed branded (usually, proprietary) medication, which generally happens at pharmacy level.

\(^2\) A reference price is the price that will be reimbursed by the State for a medicine (in a group of designated interchangeable medicines). Where a patient chooses not to receive a reference priced medicine, the patient must pay any difference between the reference price and the price of the chosen medication. This additional payment is known as a co-payment.
years, on the topic of patient perceptions of generic medicines [8-25], indicating that this is a relatively under-explored area internationally.

A 1997 report prepared for the then Minister for Health in Ireland, describing a previous attempt by the Irish government to increase usage of generic drugs, contains some historical perspective on Irish patient attitudes to generic medicines [26]. Specifically, the report stated that over half of the patients surveyed indicated a willingness to consume less expensive versions of medicines and that 83% were happy with the outcome of medication changes (to a generic drug) [26]. However, in the intervening time period, usage of generic medicines has not significantly increased (from approximately 22% in 1997) and Ireland’s usage of generic medicines has remained amongst the lowest in Europe with observed prescribing rates in 2012 as low as 19% [4, 27, 28].

With Ireland on the cusp of a major modification in healthcare practices (that is, the introduction of generic substitution and reference pricing, for the first time), there are many potential hurdles to be overcome [29]. To determine what challenges might arise as a consequence of patient opinions, the objective of this study was to assess how generic medicines were perceived amongst this critical stakeholder group, in the time leading up to the enactment of the new legislation.
Methodology

Recruitment and survey interviews

Approval of the design and conducting of this study was granted by the Ethics Committee of the Irish College of General Practitioners (ICGP).

Patients were recruited from practices of general practitioners (GPs) affiliated with the University of Limerick’s Graduate Entry Medical School and from community pharmacies. Patients, from both urban and rural locations (throughout the South/South-East of Ireland and therefore broadly reflective of Ireland’s socio-demographic profile), were approached, in person, and invited to participate in the study. All Patients present in the GP surgery waiting room/community pharmacy were invited, orally, to participate. If a willingness to participate was expressed, the study was explained to them verbally, a written explanation (patient participation leaflet) was provided and they were then entered into the study. As per the granted ethical approval, agreement to participate in the study was taken as patient consent (no signed consent forms were required). Patients waiting to see their GP were interviewed on the day (in a private consultation room). Those recruited from community pharmacies were generally interviewed at a later date, either face-to-face or via telephone (as arranged when consent to participate was given).

All interviews were performed with consenting patients between November 2012 and April 2013. (The primary author performed the interviews. The interviewer had formal training on design of questionnaires and completion of interviews and is also a professional lead auditor of quality management systems with over 15 years of experience). Interviews were conducted until data saturation had been achieved. The study instrument was informed by a recently published review of the usage of generic medicines and how policy changes to promote the use of generic medicines may affect healthcare provision [4]. Interviews, which were recorded (with each interviewee’s
permission), were primarily semi-structured and based on a series of questions to which open, or qualitative, answers could be given (Table 1). (Please note that in the case where a participant demonstrated that they did not clearly understand what a generic medicine was after the first two questions, an explanation was provided, and further questions were only asked after the interviewer had ascertained that the participant had a correct understanding). Further questioning or discussion could be completed, if required, to more fully elucidate participant views. Additional quantitative assessment of opinions was completed by use of a series of fifteen structured, closed questions to which participants could select from pre-defined answers (Table 2). In this instance, a five-point Likert scale [30] was used with a single response allowed for each question, selected from: Strongly Agree, Agree, Neutral, Disagree and Strongly Disagree. This mixed-methods approach was adopted in order to maximise data gathering using both quantitative scales and provision of opportunity for patients to volunteer free commentary on the topic. Furthermore, participants were offered the opportunity to freely express any additional opinions or views at the end of each interview.

**Analysis of data**

Interviews were transcribed, verbatim and imported into NVivo (version 9) for analysis. Transcripts were coded for themes relating to interviewee opinions, perceptions and behaviours, including any other emerging themes, and the results were analysed using Nvivo. To facilitate visualisation and understanding of the numbers of participants holding the perceptions/behaviours that were coded into specific themes, these were expressed as a percentage of the total number of participants. Analysis of quantitative data were completed using SPSS (version 20).
Participants

Forty-two (42) patients were interviewed. Patient group demographics are described in Table 3.

Results

Familiarity of patients with generic medicines

Nearly a third, 31% (13/42), of patients interviewed stated that they had no knowledge of generics, or “no idea what they were”. Of those, 39% (5/13) of patients confused the word “generic” with “genetic” when asked to explain what they believed a generic medicine to be. This misunderstanding became obvious as some patients answered positively that they had heard of generics, but could not provide an explanation as to what a generic medicine was, often speaking about genetic illnesses, for example:

   Interviewer: *Have you ever heard of generic medicines?*
   
   Patient (Female, aged 40-49 years): *I have.*
   
   Interviewer: *Ok and if you had to explain, in your own words, what your understanding of a generic medicine is, what would you say?*
   
   Patient: *Something that’s passed through, an illness that’s passed through families. Genes, that kind of thing and medicines to treat it.*

Additionally, 31% (13/42) of patients had no knowledge as to whether they had ever taken a generic medicine in the past.

Opinions regarding quality, safety and efficacy of generic medicines (Table 2)

Patients’ opinions showed a certain lack of confidence in generics; with 24% holding the view that generics were of a poorer quality than originators and in the region of a fifth...
(18%) to a quarter (26%) of patients (Table 2: statements 6 and 4, respectively) being of the view that generics do not work as well as originator products:

- Well I'd imagine the branded medicine would be more tested and that you'd probably get a better result from it. Female, aged 50-64 years.

- Personally I think that the generic medicine is maybe not as potent as the original medicine, for various different reasons, they're manufactured more cheaply so I think possibly that the products that go into them are sourced from a cheaper source, so I think maybe that they're not as good as the original. Female, aged 40-49 years.

Nearly a fifth, 18%, of patients were unsure as to whether generics were as safe as originators and 29% of patients explicitly stated that they believed generics were manufactured to a poorer quality than originator medications. Up to 42% of patients held the view that generic medicines are cheaper because they are of inferior quality to originators (table 2: statement 13) (This is an amalgamation of the SA/A and N responses, the phrase “up to” indicates the maximum percentage of respondents who could hold this view).

...[the generic is not as good] because it’s cheaper to produce and maybe, that the same quality of ingredients that’s in it, they’re not the same quality as the [originator]...Female, aged 50-64 years.

- I don't know what actually goes into medicines or tablets but if they're not the good brand, there must be cheaper stuff that they're putting in or that they're not putting in most of the ingredients or other stuff. Female, aged 30-39 years.

Preferences for branded medication

Patients exhibited a high level of trust in their GPs as, despite the opinions expressed above, 90% (34/38) of patients stated that they would be happy to take a generic
medicine if prescribed by their GP. In contrast, 24% (9/38) of patients expressed a preference for the originator medication, if offered a choice. 19% (8/42) of patients stated an explicit belief that the branded medication was better than a generic formulation.

... I would be inclined to think [the generic] would be inferior to the branded one.

Female, aged 50-64 years.

Views regarding cost of generic medicines

Patients who provided an opinion as to why generic medicines may be less expensive than originator medicines stated licencing expiration and introduction of competition as the most common factor: 29% (12/42). Other opinions expressed were: because with a generic the consumer was no longer “paying for the name” 17% (7/42); that generics come from a “cheaper country” 7% (3/42); that “cheaper” (implying a lower standard than the originator) ingredients go into them 12% (5/42); and because packaging was not as good 5% (2/42).

Opinions of new legislation

A majority, 86% (36/42), of patients expressed opinions in favour of generic substitution. 29% (12/42) additionally expressed the opinion that they should be informed of any substitution and that a substitution should not take place without their consent. A majority of patients (86% - 36/42) were also in favour of reference pricing, stating that it made sense and was necessary for cost-savings for the country (the reference price is the reimbursement price of a medicine, set by the government, which it will reimburse to pharmacies for patients on publically funded drug schemes who have been dispensed that medicine).
- I actually strongly agree with [reference pricing] because people, on the medical card system, don’t understand how expensive medication is and take it for granted. So I think that if you want a particular brand name... if you insist, the onus should be on you to pay the difference. Female, aged 30-39 years.

While a majority (71% - 30/42) of patients were of the opinion that co-payment was reasonable (the co-payment is a payment that can be made, over and above the reference price, by a patient on a publically (i.e. State) funded drug scheme who wishes to receive a medication which is more expensive than the reference priced medicine), they also stated that they would probably never make a co-payment (21% - 9/42), that is, they would accept the reference priced medicine. Moreover, 17% (7/42) of patients stated that there should be some way for patients not to have to make the co-payment where there were genuine, medical reasons for them needing to take the originator (which is allowed for in the Act, but of which they were unaware; possibly indicating that, while in favour of legislation in principle, they are generally ill-informed as to the detail and, therefore, of the full impact of the new system being implemented).

Information available to patients

None of the patients interviewed reported ever having been given any specific information by their GP or pharmacist which explained to them what a generic medicine was, and how a generic might differ from the originator brand.

- The only time I've ever got [information] was when the pharmacist actually offered me the generic version and the only explanation I got was “I'm giving you the generic version because it's cheaper”. That was the only information. Male, aged 50-64 years.

A small number, 10%, of patients (4/42) referred to a need for education to be provided regarding generic medicines. Half of patients interviewed (21/42) stated that a leaflet or
similar with such information would be useful to them, provided that it was written in an easy to understand manner, with no technical wording or jargon used.

- *I think there’s been a genuine lack of information about generic medicine, across the board and its been very much, I think, government policy not to inform the general population about generic medicine and about the option of having generic medicines and its only now that the country is broke that it’s forced to look at cheaper alternatives.* Male, aged 40-49 years.

**Concerns about variation in appearance of generic medicines**

Safety concerns were expressed by 10% (4/42) of patients, in relation to the varying appearance of generics and the impact that this can have on patients. Several anecdotes were provided regarding the confusion that can be caused – particularly in relation to elderly family members – when the appearance of their medications changed each time they refilled a prescription. Indeed, one patient told a story of her mother needing to be hospitalised after confusing two different medications, due to the appearance of the tablets being so similar, when they had, in the past, been different colours.

- *I know myself that my mother is getting generic medicines now instead of the original brand … but she does get a bit confused as to why she’s getting this instead of something else … she’s used to taking a particular tablet and then suddenly she’s being given something else and they’re not the same, [older people] don’t realise that it’s the same thing because it’s called something else.* Female, aged 40-49 years.
Influence of the pharmaceutical industry

A small number of patients (7% - 3/42) expressed the opinion that they felt that doctors were being influenced by medicines’ manufacturers to prescribe brand name drugs in favour of less expensive alternatives.

- *I think [branded medicines] are being forced on us by doctors and especially when you see ... the brand all around doctors surgeries as well ... I think that doctors are nearly encouraged by pharmaceutical companies, I don’t know if there’s any monetary benefit to it but I think they’re encouraged to give us branded drugs.* Female, aged 18-29 years.
Discussion

There have been numerous publications focused on generic medicines: their introduction, subsequent use and aspects of efficacy or otherwise [4]. However, there has been relatively limited literature regarding the attitudes of patients towards these products in the last decade. While studies have originated from Norway (patients attitudes to generic substitution) [31], Finland (preferences of patients for generic and branded OTC (over-the-counter) pain medicines) [14], Portugal (patient perceptions of underuse of generics and their attitudes towards generic substitution) [21], South Africa (consumer perceptions of generic drug quality compared with actual drug quality) [20, 32], New Zealand (patients’ perceptions, knowledge and attitudes regarding generic medicines and investigation of patients’ attitudes towards generic substitution of oral antipsychotics) [10, 23], Iraq (consumers’ knowledge relating to generic medicines) [25], and the United States (patient knowledge of, and attitudes relating to, formulation switching of antiepileptic drugs) [33], amongst others, the perceptions of Irish patients with regard to generic medicines have not been published previously. Moreover, only four other interview-based studies of the opinions of patients regarding generic medicines could be found (PubMed search, July 2013) and the number of participants in this study is comparable to those studies from Iraq [25], Norway [13], and the United States [34, 35], which interviewed 14, 83, 30 and 50 participants, respectively.

While this study redresses that gap in the literature, an initial interesting observation was that while about two-thirds (69%) of Irish patients had a correct understanding of what a generic medicine is, patient confusion existed regarding the words “generic” and “genetic”. This may result in overestimation of the general public’s understanding of generic medicines in surveys that do not delve beyond an initial awareness.
As in other studies, from the United Arab Emirates [8], Norway [12, 31], Finland [14], France [16], and a significant proportion of the patient cohort expressed mistrust in generic medications and a preference for branded medication. Patients, however, demonstrated a high level of trust in their GP, and had faith in what is prescribed for them by their GP, even when the patients themselves held the opinion that generics are inferior to originator medications. This also mirrors results reported elsewhere regarding patient trust in prescribing by their physicians [21].

- *Well if the doctor would prescribe the medicine and say it's as good as the branded I would take it.* (Illustrative comment by female participant, aged 18-29 years).

- *Yeah if my doctor gave it I would [take a generic] because I'd trust my doctor, but if it was a strange doctor I might be a bit (pauses, indicating reticence) but own doctor I'd take it yeah.* (Illustrative comment by female participant, aged 50-64 years).

With respect to information about generic medicines and its availability to patients, patients expressed the opinion that any leaflets/information etc. needed to be written in such a way that they could be easily understood and without the use of jargon or scientific/technical terms. Considering that, despite healthcare professionals’ best efforts, educational interventions with patients can often be unsuccessful [36], ensuring that such information is readable and understandable by the general public is essential. Indeed, our group has recently published a novel tool, based on optimised quality of information and reading ability, for development of websites providing healthcare information that could be utilised in the provision of such information to patients [37].

Analogous to results from New Zealand [10] and Finland [38], a substantial number of patients were seen to have negative attitudes towards generics and, therefore, there
remains considerable scope to educate the patient group, thereby improving their confidence in, and hence acceptance of, generic medicines.

- *I suppose my understanding is that you have what you call the elite or top end medicine and then you have what you call generic medicine which would be a step down from those…* (illustrative comment by male participant, aged 40-49 years).

This has the potential to be pivotal not only for the success of the new legislation, in an Irish context, but also for a continued improvement in usage of generics worldwide. Educational interventions are recognised as being a vital requirement to ensure patient understanding of generic medications [20, 21, 25, 32, 39] (e.g., such products often have a different visual presentation to the originator, knowledge of which could be valuable in preventing issues of confusion and medication errors associated with a switch to a generic formulation). Additionally, patients might benefit from improved understanding that generic medicines are not identical in content to the originator; indeed, it has been shown that differences in excipients can result in significant issues for some patients [33, 40, 41].

A possible limitation of this study is the fact that participants’ opinions were gathered in differing interview settings, that is, some participants were interviewed face-to-face, in a GP surgery, and others were interviewed over the telephone. Given that location of interviews may have an impact on participants [42] this might have influenced the data gathered in this study. However, review and comparison of the themes emerging from participants interviewed in different settings did not show any substantial difference in the opinions, perceptions and behaviours expressed between participants interviewed in different settings. Furthermore, while the authors acknowledge that quantification of qualitative data is sometimes contentious, we chose to adopt this approach in order to best provide easy visualisation of results and offer a more comprehensive insight into
the patient perspective. The strengths of such an approach have been discussed by Schonfelder in 2011 [43].

Future work in this area, as suggested by Timonen et al in their work on similar changes in Finland [44], would be to evaluate the changes made several years after its introduction, from a number of perspectives. In particular, it would be interesting to examine the usage of “Do Not Substitute” (DNS) prescriptions to determine if patient preference for branded medication has transferred to a demand for DNS prescriptions from physicians and, indeed, if physicians yield to this demand. Given that the intent of the new Act is to reduce the drugs bill for the Irish state, over-use of DNS prescriptions has the potential to negate some of the financial benefits expected to accrue.

Conclusions

It is clear from this study that areas for improvement of perceptions of generic medicines still remain. In an era when usage of generic medicines is an ever-increasing and necessary part of cost-control in healthcare provision, elucidation of the root causes of persisting negative opinions about generic medicines is important to determining the actions to be taken to mitigate them. Determining such root causes must, however, be done with care, as high-level surveys which do not investigate the deeper understanding of study participants may overestimate the level of understanding of, or familiarity with, generic medications (or any other topic). Provision of information/education to patients, in a jargon-free, easy to understand manner, which explains the differences as well as the similarities, including the equivalency of generic medicines, may be key to improving patient opinions and negating the mistrust which the patient cohort exhibits.
Acknowledgements

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The authors each declare that they do not have any conflicts of interest.

SD designed the study, carried out the interviews and data analysis. SD was the primary author of the manuscript.

BS approved the design of the study and provided critical review of the manuscript.

CD approved the design of the study and provided critical review of the manuscript and is the overall guarantor.

WC approved the design of the study and provided critical review of the manuscript.
References:


## Table 1 – Study Instrument: Semi-Structured Interview Questions

<table>
<thead>
<tr>
<th>Question</th>
<th>Answer type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Have you ever heard of generic medicines?</td>
<td>Y/N</td>
</tr>
<tr>
<td>Do you know what a generic medicine is?</td>
<td>Y/N</td>
</tr>
<tr>
<td>Can you please explain what your understanding of a generic med is?</td>
<td>Free</td>
</tr>
<tr>
<td>Or - What is your best guess as to what a generic medicine is?</td>
<td></td>
</tr>
<tr>
<td>Have you ever taken a generic medicine?</td>
<td>Y/N/DK</td>
</tr>
<tr>
<td>What do you <em>believe</em> about how generic medicines compare to brand-name medicines?</td>
<td>Free</td>
</tr>
<tr>
<td>Have you ever been given a flyer/handout or any other information on generic medicines by your GP or Pharmacist?</td>
<td>Y/N</td>
</tr>
<tr>
<td>If yes, what was it you were given?</td>
<td>Free</td>
</tr>
<tr>
<td>What information did you get from what you were given?</td>
<td>free</td>
</tr>
<tr>
<td>What was your opinion of the information you were given?</td>
<td>free</td>
</tr>
<tr>
<td>Did you feel you fully understood the information?</td>
<td>Y/N/free</td>
</tr>
<tr>
<td>If no, do you believe that being given some literature explaining what generic medicines are would be [have been] useful to you?</td>
<td>Y/N</td>
</tr>
</tbody>
</table>

*Generic Substitution*

At the moment, a pharmacist can only supply you, the patient, with whatever brand of a medicine is prescribed by your doctor. The government is in the process of introducing new legislation that will allow pharmacists to dispense lower cost generic versions of a medicine, if a doctor prescribes a more expensive version.

**What is your opinion of this? What do you think about this?**
**Reference Pricing**

When this new law comes into force, there will be a “reference price” set for groups of medicines that will be defined as being interchangeable – meaning that they have the same active ingredient and can be used to treat the same illness. In this case, (for eligible patients – GMS or DPS) the state will only reimburse the cost of the reference price for any given medicine, and if you want to get a different version of the same medicine that costs more, you will have to pay the difference.

What is your opinion of this? How do you feel about this? What do you think of this change?
Table 2 – Study Instrument: Quantitative assessment questions and responses of patients

Of 42 patients interviewed, 4 declined to answer these questions as they felt that they did not have enough knowledge or information to provide answers. Therefore, n=38 patients for this segment.

<table>
<thead>
<tr>
<th>Do you strongly agree, agree, neither agree nor disagree, disagree, strongly disagree with the following statements:</th>
<th>Patients n=38</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SA/A¹</td>
</tr>
<tr>
<td></td>
<td>n</td>
</tr>
<tr>
<td>1 Generic medicines are generally of the same quality as originator medicines.</td>
<td>31 82</td>
</tr>
<tr>
<td>2 Generic medicines are generally poorer quality than originator medicines.</td>
<td>9 24</td>
</tr>
<tr>
<td>3 Generic medicines are generally better quality than originator medicines.</td>
<td>0 0</td>
</tr>
<tr>
<td>4 Generic medicines work as effectively as originator medicines.</td>
<td>28 74</td>
</tr>
<tr>
<td>5 Generic medicines work better than originator medicines.</td>
<td>0 0</td>
</tr>
<tr>
<td>6 Generic medicines do not work as well as originator medicines</td>
<td>7 18</td>
</tr>
<tr>
<td>7 Generic medicines may be dangerous compared to originator medicines</td>
<td>2 5</td>
</tr>
<tr>
<td>8 Generic medicines are as safe as originator medicines.</td>
<td>31 82</td>
</tr>
<tr>
<td>9 Generic medicines are manufactured to the same quality as originator medicines.</td>
<td>26 68</td>
</tr>
<tr>
<td>10 Generic medicines are manufactured to a poorer quality than originator medicines</td>
<td>11 29</td>
</tr>
<tr>
<td>11 Generic medicines are manufactured to a higher quality than originator medicines</td>
<td>0 0</td>
</tr>
<tr>
<td>12 Generic medicines are cheaper to buy than originator medicines.</td>
<td>36 95</td>
</tr>
<tr>
<td>13 Generic medicines are cheaper because they are of inferior quality to originator medicines.</td>
<td>11 29</td>
</tr>
<tr>
<td>14 If I were ill, I would be happy to take a generic medicine if my doctor prescribed it for me.</td>
<td>34 90</td>
</tr>
<tr>
<td>15 If I were ill, I would prefer to take an originator medicine rather than a generic medicine, even if it is more expensive.</td>
<td>9 24</td>
</tr>
</tbody>
</table>

¹Strongly Agree/Agree
²Strongly disagree/Disagree
³Neutral/No opinion
Table 3 – Demographics

<table>
<thead>
<tr>
<th>Demographic</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender</strong></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>12</td>
</tr>
<tr>
<td>Female</td>
<td>30</td>
</tr>
<tr>
<td><strong>Patient status</strong></td>
<td></td>
</tr>
<tr>
<td>Private (^1)</td>
<td>18</td>
</tr>
<tr>
<td>Public (^2)</td>
<td>24</td>
</tr>
<tr>
<td><strong>Age profile</strong></td>
<td></td>
</tr>
<tr>
<td>18-29</td>
<td>6</td>
</tr>
<tr>
<td>30-39</td>
<td>9</td>
</tr>
<tr>
<td>40-49</td>
<td>8</td>
</tr>
<tr>
<td>50-64</td>
<td>12</td>
</tr>
<tr>
<td>65+</td>
<td>7</td>
</tr>
</tbody>
</table>

\(^1\) Self-paying

\(^2\) That is: in receipt of a General Medical Services card (For clarity: In Ireland, the General Medical Services (GMS or medical card) scheme is available to persons who are unable, without undue financial hardship, to arrange general practitioner medical and surgical services for themselves and their dependents. Being in receipt of a medical card allows the holder to receive a free (or subsidised) general medical service).
Chapter 8

A Method for the Design and Development of Medical or Health Care Information Websites to Optimize Search Engine Results Page Rankings on Google.

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Type of paper:
Original Research

Title:
A Method For Design and Development of Medical or Healthcare Information Websites to Optimise Google™ Search Engine Results Page (SERP) Rankings.

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Abstract

Background
The Internet is a widely used source of information for patients searching for medical/healthcare information. While many studies have assessed existing medical/healthcare information on the Internet, relatively few have examined methods for design and delivery of such websites – particularly those aimed at the general public.

Objective
This study describes a method of evaluating material for new medical/healthcare websites, or for assessing those already in existence, which is correlated with higher rankings on google.com Search Engine Results Pages (SERPs).

Methods
A Website Quality Assessment (WQA) tool was developed using criteria related to the quality of the information to be contained in the website in addition to an assessment of the readability of the text. This was retrospectively applied to assess existing websites that provide information about generic medicines. The reproducibility of the WQA tool and its predictive validity were assessed in this study.

Results
The WQA tool demonstrated very high reproducibility (intraclass correlation coefficient = 0.95) between two independent users. A moderate to strong correlation was found between WQA scores and rankings on google.com SERPs. Analogous correlations were seen between rankings and readability of websites as determined by Flesch Reading Ease and Flesch-Kincaid Grade Level scores.

Conclusions
The use of the WQA tool developed in this study is recommended as part of the design phase of a medical or healthcare information provision website, along with assessment
of readability of the material to be used. This may ensure that the website performs better on google.com searches. The tool can also be used retrospectively to make improvements to existing websites; thus, potentially enabling better google.com search result positions without incurring the costs associated with Search Engine Optimisation (SEO) professionals or paid promotion.

**Keywords**

Google, generic drugs, Internet, medical informatics, healthcare information, patient education, comprehension (readability), Google SERP, website development, quality assessment.
Introduction

A multitude of studies have assessed the use, quality and/or availability of medical/healthcare information on the Internet in areas as diverse as: inflammatory bowel disease [1], orthodontistry [2, 3], pain [4], cancer [5-7] and mental health [8, 9], amongst many others. Such studies often look at information available to, and used by, people in particular geographic areas, for example: paediatric asthma in Saudi Arabia [10], preconception care in Italy [11], and medical information in Brazil [12] and Portugal [13]. A PubMed search for research into online medical information, including, for example, use of resources such as Wikipedia or Google™ in medical education and availability of information for patients, provides thousands of search results. This is indicative of the fact that the Internet has become a source of medical information for patients and healthcare professionals alike, as evinced by the increasing prevalence of use of the Internet and social networking associated with “web 2.0” for information sourcing and sharing online [14].

In the area of generic medicines, misconceptions and misinformation exist that are easily disseminated and perpetuated online, and, given that healthcare professionals have expressed poor opinions of generics in the past [15], it is, therefore, challenging to communicate accurate information to the general public about the medicines that they are taking. There is a necessity to provide accurate information, to dispel myths and to counter misinformation, but also to present the material in a manner that is accessible to the intended audience. For example, it has been reported that, in the case of patients particularly, myths and uncertainties about generic medicines abound, and that accurate information can be difficult to come by [16].

A good quality medical or healthcare information website could be defined as one which contains accurate and unbiased information on all aspects of the topic (both positive and negative) for which the website is published, in conjunction with the ability of the
website to be easily read and understood by its target audience. Where the audience is intended to be the general public, readability of the website will be a key factor in its success (as defined by the number of hits the website receives, indicative of its ranking on Internet search engine results). After all, if a website contains exemplary information, but cannot be easily read and understood by its audience, it is possible for it to go largely undiscovered in the plethora of information available on the Internet.

This study was concerned with non-advertised or promoted websites (i.e., rankings on a Search Engine Results Page (SERP) which are not there as a result of a paid advertisement or promotion, but rather are ranked and returned by Google™'s algorithms).

While the availability and accuracy of existing online medical/healthcare information continues to be studied, much less work appears to have been performed in the area of development of medical information websites - in particular websites aimed at providing accurate and unbiased medical information to the general public (a PubMed search – done 22 February 2013 using the search term development medical information website – returned 28 articles which were specifically related to the topic of development of medical/healthcare information websites).

The objective of this paper was to provide a method for the planning of information to be included in medical information websites, and for representing that information in a readable manner. As Search Engine Optimisation (SEO) can be a critical factor in ensuring top-ranking search engine results [17] and, given that the cost of using potentially expensive online advertising or SEO professionals in order to promote a website may be prohibitive for government or advocacy groups wishing to impart good quality medical/healthcare information, use of the tools and techniques described in this paper will not only ensure the quality of the information in the website but may
also provide the website with an improved chance of being returned to a searcher in a higher ranking on a Google™ SERP, without incurring significant additional cost.
Methods

Rationale

To ensure a high quality medical information website, two factors should be considered in its development: (i) the information to be contained therein (quality, accuracy, comprehensiveness, balance, impartiality, etc.) and (ii) the ability of the information to be read and understood by the target audience.

On the basis of the above an assessment tool was developed that may be used to prospectively design the content of an optimised website. This study reports the composition of that tool and its validation through retrospective assessment of existing sites.

Information Gathering and Website Quality Assessment (WQA) Tool

Development

A tool for assessment of websites imparting information on generic drugs was developed. This Website Quality Assessment (WQA) tool consisted of a series of yes/no type questions, where a point was awarded for positive or correct information – see Table 1. No points were awarded for information lacking, or for inaccurate information. Questions that cannot be answered were designated “not applicable” (N/A) and no score awarded. An overall WQA score for each website was totalled from the scores assigned to each assessment question.
Table 1 – Website Quality Assessment [WQA] for Assessing Generic Medicines Information Websites

<table>
<thead>
<tr>
<th>Question</th>
<th>Answer and Score</th>
<th>WQA Score awarded</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Does the site give an explanation as to what a generic medicine is?</td>
<td>Yes = 1, No = 0</td>
<td></td>
</tr>
<tr>
<td>2. Is this explanation correct?</td>
<td>Yes = 1, No = 0</td>
<td></td>
</tr>
<tr>
<td>(i.e. equivalent in dose, strength, route of administration, safety, efficacy, and intended use)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. If so, is the explanation of a generic medicine readable and understandable by a non-scientist?</td>
<td>Yes = 1, No = 0</td>
<td></td>
</tr>
<tr>
<td>4. Are examples given of generic medicines? E.g. example of a proprietary medicine that also state their counterpart generic medicine?</td>
<td>Yes = 1, No = 0</td>
<td></td>
</tr>
<tr>
<td>5. Is bioequivalence mentioned in the website?</td>
<td>Yes = 1, No = 0</td>
<td></td>
</tr>
<tr>
<td>6. Is bioequivalence explained?</td>
<td>Yes = 1, No = 0</td>
<td>N/A</td>
</tr>
<tr>
<td>7. If so, is the explanation of bioequivalence correct?</td>
<td>Yes = 1, No = 0</td>
<td>N/A</td>
</tr>
<tr>
<td>8. If so, is the explanation of bioequivalence readable and understandable by a non-scientist?</td>
<td>Yes = 1, No = 0</td>
<td>N/A</td>
</tr>
<tr>
<td>9. Is the cheaper price of generics referred to?</td>
<td>Yes = 1, No = 0</td>
<td></td>
</tr>
<tr>
<td>10. Is an accurate reason for the cheaper price of generics given?</td>
<td>Yes = 1, No = 0</td>
<td>N/A</td>
</tr>
<tr>
<td>11. Is any inaccurate information regarding the cheaper price of generics given?</td>
<td>Yes = 0, No = 1</td>
<td>N/A</td>
</tr>
<tr>
<td>12. Are examples given of the actual price difference between generics and proprietary medicines, or of the amount of money that can be saved by use of generics?</td>
<td>Yes = 1, No = 0</td>
<td></td>
</tr>
<tr>
<td>13. Is reference made to the fact that approved, equivalent generic meds can have a different appearance (colour, shape etc.) different taste/smell or different inactive ingredients?</td>
<td>Yes = 1, No = 0</td>
<td></td>
</tr>
<tr>
<td>14. Are narrow therapeutic index [NTI] drugs mentioned?</td>
<td>Yes = 1, No = 0</td>
<td></td>
</tr>
<tr>
<td>Question</td>
<td>Answer and Score</td>
<td>WQA Score awarded</td>
</tr>
<tr>
<td>-------------------------------------------------------------------------</td>
<td>------------------</td>
<td>-------------------</td>
</tr>
<tr>
<td>15. Is the difference between NTI and non-NTI drugs explained?</td>
<td>Yes = 1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No = 0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>16. Is there accurate information given on how generic bioequivalence, or generic manufacturing may affect NTI drugs?</td>
<td>Yes = 1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No = 0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>17. Is any inaccurate information given regarding NTI drugs?</td>
<td>Yes = 0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No = 1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>18. Are “pros” of generics mentioned? [e.g. lower price for same safety &amp; bioequivalence etc…]</td>
<td>Yes = 1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No = 0</td>
<td></td>
</tr>
<tr>
<td>19. Are any “cons” of generics mentioned? [e.g. adverse events to dissimilar excipients etc…]</td>
<td>Yes = 1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No = 0</td>
<td></td>
</tr>
<tr>
<td>20. Is the difference between proprietary and non-proprietary names mentioned?</td>
<td>Yes = 1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No = 0</td>
<td></td>
</tr>
<tr>
<td>21. Is the explanation given for the difference between proprietary and non-proprietary names accurate?</td>
<td>Yes = 1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No = 0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>22. Generic prescribing mentioned and explained accurately?</td>
<td>Yes = 1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No = 0</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TOTAL WQA SCORE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flesch Reading Ease Score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flesch Kincaid Grade Level</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

In development of the WQA tool, the following criteria were used:

(i) Listing of the questions likely to be asked by the searcher

(ii) What myths or misinformation exist on the topic, which may need to be dispelled or corrected?

(iii) What information could be required by the searcher in order to assist in making informed decisions

(iv) Relevant comparisons or analogies that might help in understanding of the topic by a non-scientist or clinician

(v) Any associated or corollary information from other related topics or areas that might be helpful to support understanding of the topic in question.
The number of assessment questions will be determined by the topic in question and is not fixed. However, all areas in the five criteria steps noted above should be covered in the WQA questions used.

Validation of the WQA tool

To validate the tool, searches were performed in google.com and a number of the resulting hits in the SERPs returned were assessed using the 22-question Generic Medicines WQA (Table 1). The search was physically done in several English-speaking countries, using computers with Internet Protocol (IP) addresses in those countries, in order to determine if there was any country-to-country (or geographic) variability. The countries in which searches were performed were: United States, Canada, Ireland, Great Britain and Australia. The search term used was identical in all cases: “generic drug OR medicine” (without the quotes). All searches were performed during March and April of 2012 and a total of 24 distinct websites were assessed.

To measure reproducibility of use of the tool, each of the websites was independently assessed by two different raters.

Assessment of Website Readability

Readability of text is an important issue, especially in the medical domain. For this study readability of text was assessed using two methods: (i) Flesch Reading Ease score and (ii) Flesch-Kincaid Grade Level, however it is worth noting that other readability evaluation methods have also been used in the assessment of medical texts [18].

A minimum of a 100-word sample of continuous text was selected at random from the website text and pasted into Microsoft Word™. This text was then analysed using the Readability Statistics in the Word™ application.
Word™️'s Flesch Reading Ease score is based on a formula developed in 1948 by Rudolf Flesch [19]. It is computed using the average number of syllables per word and words per sentence. Syllables-per-word is a measure of word difficulty. Words-per-sentence is an indicator of syntactic complexity.

The Flesch Reading Ease scale ranges from zero to 100. Zero to 50 is very difficult to difficult reading. Eighty and above is easy to very easy reading. Flesch himself set the minimum score for plain English at 60 [19]. Microsoft™️'s documentation encourages authors of standard documents to aim for a score of 60 to 70 [20, 21].

The Flesch-Kincaid Grade Level, which was developed in 1975, measures the readability of a document based on the minimum education level required for a reader to understand it [22]. Microsoft™ recommends aiming for a Flesch-Kincaid score of 7.0 to 8.0 for most documents. According to a 1993 study, the average adult in the U.S. reads at the seventh-grade level and the authors of that study recommended that materials for the public be written at a fifth- or sixth-grade reading level [20].

**Statistical Analyses**

The mean and standard deviation of the differences between the two reviewers for all three tools (WQA, Flesch Reading Ease score and Flesch Kincaid Grade level) were used to calculate limits of agreement which are represented graphically in Bland-Altman plots. The intraclass correlation coefficient (ICC) was used to measure reproducibility. Spearman’s correlation coefficient ($r_s$) was used to measure the association between the ranking of websites with WQA scores and readability assessments. Absolute values of $r_s > 0.3$ were considered to represent moderate correlations, $> 0.5$ were considered strong correlations. The scores from the developer of the assessment tool (SD) were used in the correlation analyses. The correlation between
ranking of websites and WQA scores was also used to demonstrate the predictive validity of this newly developed assessment tool.
Results

Validation of the WQA tool

Statistical analysis of the two independent raters (SD and NC) using Bland-Altman plots showed that, for WQA assessments of the websites, the mean difference (SD minus NC) represented by the solid black line in Figure 1a was zero (Std Dev = 1.18) indicating perfect agreement on average. The median difference was also zero (range –3 to 2). Only one observation was outside the limits of agreement - this website was a list of brand name medicines alongside the names of their generic counterparts. One rater performed the WQA based on this list, whereas the second rater looked for information in other pages of the website, thus accounting for the difference in WQA ratings awarded. An intraclass correlation coefficient (ICC) value of 0.94 indicated excellent reproducibility between different users.

Similar analysis of the readability of the websites using Flesch Reading Ease score (on a scale of 0 to 100) and Flesch-Kincaid Grade Level (on a scale of 1 to 18) - Figure 1b and c - showed comparable levels of agreement. The mean difference (SD minus NC) for reading ease score is 4.66 (Std Dev = 12.06) indicating SD was scoring slightly higher than NC on average. The mean difference (SD minus NC) for grade level was -1.79 (Std Dev = 2.86) indicating that SD was scoring slightly lower than NC on average. One observation in each case was outside the limits of agreement. However, as each rating was independent, different sections of text were likely to be taken from each of the websites assessed. This variation in the text taken most likely accounted for the single observation outside the limits of agreement. An ICC value of 0.71 for Flesch Reading Ease score and 0.63 for Flesch-Kincaid Grade level demonstrate moderate to strong reproducibility, particularly given the subjectivity of this type of assessment, and the possible variability in the text selected by reviewers for assessment.
Overall, the WQA and readability scores demonstrate acceptable reproducibility of the tools when used by more than one rater.

**Correlation between WQA score and SERP ranking**

Scatter plots of WQA score against rankings on google.com SERPs in different regions worldwide (US, Canada, Ireland, UK and Australia) are given in Figure 2. Using Spearman's correlation coefficient, a moderate to strong correlation between a WQA score and ranking on google.com SERPs could be seen (Table 2). The observed relationship was seen in google.com searches done in the different regions worldwide indicating that the correlation occurs regardless of the location or IP address of the searcher's computer. The strongest correlation ($r_s = -0.67$), was seen in the google.com search performed in the US.

**Table 2 Correlation Between WQA, Reading Ease Score And Grade Level With Ranking Using Spearman's Correlation Coefficient ($r_s$)**

<table>
<thead>
<tr>
<th>Domain</th>
<th>n</th>
<th>WQA Spearman's $r_s$</th>
<th>Flesch Reading Ease Score Spearman's $r_s$</th>
<th>Flesch Kincaid Grade level Spearman's $r_s$</th>
</tr>
</thead>
<tbody>
<tr>
<td>US / .com</td>
<td>7</td>
<td>-0.67</td>
<td>-0.64</td>
<td>0.68</td>
</tr>
<tr>
<td>CA / .com</td>
<td>8</td>
<td>-0.38</td>
<td>-0.48</td>
<td>0.43</td>
</tr>
<tr>
<td>IE / .com</td>
<td>8</td>
<td>-0.49</td>
<td>-0.33</td>
<td>0.24</td>
</tr>
<tr>
<td>UK / .com</td>
<td>8</td>
<td>-0.38</td>
<td>-0.48</td>
<td>0.43</td>
</tr>
<tr>
<td>AU / .com</td>
<td>8</td>
<td>-0.34</td>
<td>0.29</td>
<td>-0.38</td>
</tr>
</tbody>
</table>

Therefore, use of WQA assessment questions while developing information for inclusion in a medical information website could, by corollary, be a step towards ensuring higher google.com SERP rankings and, therefore, exposure to a greater potential audience for the website.
Correlation of readability with SERP ranking

There was also a relationship, in general, between readability and ranking on google.com searches (Table 2). Flesch Reading Ease scores were correlated with the SERP ranking of the websites in each country. Again, the strongest relationship was seen in the US google.com search ($r_s = -0.64$). In general, the top ranked sites (placed 1, 2, etc.) tended to have the higher Reading Ease scores. Because of the small sample sizes in the study (at most 10 websites in each domain) and hence low statistical power, a descriptive analysis is presented and no hypothesis tests were carried out.

Additionally, scores for Flesch Kincaid Grade Level assessments were correlated with SERP ranking of the websites. In general, the top ranked sites tended to have lower Grade Level values with the most significant relationship again being seen in the US search ($r_s$ value of 0.68). Therefore, the implication is that websites with greater ease of readability are more likely to rank highly in, and therefore be accessed from, google.com SERPs.
Discussion

Prior to publication of a website, information must be gathered and written which will be disseminated to the intended audience through the website. Development and use of a specific WQA-type assessment during the design phase of a medical/healthcare information website on any topic will ensure that the information put into the website is of sufficient quality to satisfy potential searchers and users of the website. WQA can be used to assess drafts of the information to be published. Use of positive and negative scoring (positive scoring for information that is necessary, of good quality and needed to support the integrity of the website; negative scoring for any information which is inaccurate, biased or which may take from the integrity of the information) employed by WQA assessment ensures that all aspects of the information gathering initiative are accounted for during the website design.

As the internet is one of the first places a patient is likely to go when searching for medical information [23] and given that Google™ is the primary search engine in use worldwide, holding almost 90% of the global search engine market [24], corollary use of WQA could possibly lead to higher rankings on google.com SERPs for websites using this tool in their design and development.

Furthermore, this study has demonstrated that websites with greater ease of readability are more likely to rank highly in and, thereby, be accessed from, google.com searches. Therefore, inclusion of Flesch Reading Ease and Flesch Kincaid Grade Level assessments as part of the WQA enable a more comprehensive assessment of how the website might perform in google.com searches. We have demonstrated in this paper that high readability scores, and WQA scores, are more likely to lead to high google.com SERP ranking.

A limitation of this study is the small number of websites assessed. Further studies in this area could make use of technology, for example: a web crawler, to gain additional
information that could allow for clustering or commonalities across a spectrum of similar websites to be examined. A further study could evaluate sites containing similar content, but focussing on usability and accessibility – for example: are the sites well designed, are they pleasing to the eye and is the navigation user-friendly? Isolating such content from the design and visual presentation of websites would provide further insight into the usability and accessibility of medical information providing websites, which would complement the findings in this paper. Indeed, information from such a study, if done using websites focussed on generic medicines, may provide insight into the adoption and penetration of such medicines in different markets worldwide.

With about 16% of adults in the UK being described as “functionally illiterate”, meaning that they have the literacy levels at or below those expected from an 11-year old [25], and the International Adult Literacy Survey showing that one in four adults in the Republic of Ireland have problems with even the simplest of literacy tasks [26] with similar rates being seen in the US [27] and Canada [28], it is fair to say that the writing of medical information websites with this in mind may be the most important aspect in providing medical information to the general public. This point, of course, applies to all printed material (e.g., pamphlets given to patients), not just information published online. Arguably, it follows that training writers of medical information (to be disseminated to the general public, for instance) in methods of presenting simple, clear language is an important aspect in ensuring that the general public understand the information that healthcare professionals might be trying to impart to them. This becomes particularly important in light of research showing that there is often a discrepancy between the information that a physician believes a patient to have, and what the patient actually understands [29].

Language complexity as a block to accessibility of information has been recognised by Wikipedia, the 6th most commonly accessed website in the world [30] and, as a solution,
Wikipedia is available in both English and Simple English – where the Simple version is intended to be more accessible by use of simplified language and limited vocabulary. Consequently, Wikipedia guidelines on writing of the Simple version may be of use to those creating medical information websites for the general public [31].

Overall, use of the WQA tool, developed here, in the planning and preparation of material to be published in medical information websites, alongside an assessment of readability of the written material, is likely to ensure that the website subsequently ranks more highly in google.com SERPs and is, thus, more likely to be accessed, as well as read and understood, by the intended audience.
Acknowledgements

The authors would like to thank Ms. YT Chueh and Dr. Phil Hensche for their help in performing the Internet searches. This work was supported in part by a scholarship from the Faculty of Education and Health Sciences, University of Limerick, Ireland.

Conflicts of Interest

The authors have no conflicts of interest.
References


20. Using Microsoft Word's Readability Program

   [http://www.michbar.org/journal/pdf/pdf4article1467.pdf ; Archived at:
   http://www.webcitation.org/6FBcYBYCa]


   http://www.webcitation.org/6FBcwjzei]


24. Bing Overtakes Yahoo! Globally for First Time – StatCounter

   http://www.webcitation.org/6FBd5f5Zo]

25. How many illiterate adults are there in England?

   [http://www.literacytrust.org.uk/adult_literacy/illiterate_adults_in_england
   Archived at: http://www.webcitation.org/6FBdF9w4m]

27. **IALS Results** [http://nces.ed.gov/surveys/all/results.asp](http://nces.ed.gov/surveys/all/results.asp) Archived at: [http://www.webcitation.org/6FBdNgMBd](http://www.webcitation.org/6FBdNgMBd)


Abbreviations

SERP  Search Engine Results Page
WQA   Website Quality Assessment
SEO   Search Engine Optimisation
N/A   Not Applicable
IP    Internet Protocol
Addendum 1 to Chapter 8

Justification of methodology used and further research on the WQA tool described in the chapter entitled: A Method For Design and Development of Medical or Healthcare Information Websites to Optimise Google™ Search Engine Results Page (SERP) Rankings.

Purpose

The purpose of this document is to provide an academic justification for the methodology adopted in this chapter, as published in the Journal of Medical Internet Research (JMIR) in 2013, and to describe further research planned.

Background

Point three of the external examiner’s report requested: Further evaluation of the WQA tool using more raters and websites and expansion of chapter 6 to incorporate the findings of additional work.

(Note: this paper appeared as chapter 6 of the version of the thesis provided for the viva. Subsequent amendments mean that this is now chapter 7).

The aim of this work was to develop a tool to be used to assess online information on the topic of generic medicines. This type of research is well established and many tools have been developed and published over the years for assessment of specific areas of healthcare/medical information, for example: schizophrenia, cancer and drug addition, amongst many others [1-7]. As the area of generic medicines had never been the subject of such an assessment, part of the work undertaken in this thesis was to answer the
question: what does the Internet tell patients/consumers who have questions about
generic medicines?
As no specific tool existed for such an assessment, corresponding publications (such as
those referenced above) were reviewed, a comparable methodology was adopted and a
specific tool developed for the review of websites on the topic of generic medicines (the
WQA tool). Therefore, in summary, while the tool developed for use in this thesis is
novel in that it is the only published tool for the assessment of online information on
generic medicines, the general premise is one that has been utilised many times for the
assessment of online information in many different subject areas.

Rationale
This justification provides a rationale for both i) the number of raters used; ii) the
number of websites rated.

i) Number of Raters Used
The decision to use two raters was based on review of similar, reputable work
completed by multiple groups in the development of tools for evaluating online
information in areas other than those covered in this thesis. The aim of this review,
while designing the WQA tool, was to align the approach taken with other published
methodologies for assessment of medical/healthcare information provided on the
Internet.

Numerous, high-quality studies of online information, similar in principle to that
performed in this thesis, used two people (or fewer) to evaluate a newly developed tool
for assessment of information provided on the Internet [1-13]. In fact, there are several
examples of groups having a two-rater approach published, and then subsequently
repeating that methodology, successfully, in further research. Good examples of this approach can be seen in studies completed by Lawrentschuk et al [10, 14], Henderson et al [15, 16] and a Canadian group led by Leddin and Langille [6, 7, 9].

Please note that as there are many other examples of 2-rater approaches in the literature, the citations herein are chosen for illustrative purposes and represent only a portion of those available (these were chosen based on date (recent publications being preferred) and on availability of the full text of the publication through the UL library).

As per the best practices determined from the literature reviewed, the raters engaged with this thesis worked independently and were blind to each other’s results (as described, for example, by Rossler et al in their paper on YouTube information on lumbar puncture and neuroaxial block techniques, which made reference to the fact that they used PRISMA guidelines for their evaluations, that is: two independent evaluators [12]). Therefore, as the decision to use two raters was based on, and can be supported by, an accepted and often-published approach in this field of research, the methodology used is both sound and scientifically defensible.

Further research, using additional raters could add information regarding the reproducibility of the tool, however as the typical approach used by other groups was a 2-rater approach (where raters were trained in use of the tool or were subject experts in the topic under investigation and therefore able to provide an analysis of the quality of the information provided) that approach was adopted in this work also.

There are many practical issues relating to repetition of the work with additional raters – not only in the time needed to train raters in the tool, but also in the time needed to rate the websites and perform analysis of the data produced. (Also, the websites are likely have changed in the two years since this work was originally performed, and
cached versions would have to be sourced in order to compare like with like).

Specifically, while training of additional raters could be completed in several hours – for the work already completed, the raters spent approximately 15-30 minutes assessing each website. For additional raters to assess the original 24 websites it would be reasonable to estimate a requirement of between 6 to 12 hours per person. It is likely that this length of time could be significantly underestimated if raters are used who are less familiar with generic medicines and how they differ from proprietary medicines. Recruitment of raters (who are likely to have to fit this work in with other commitments), training of raters and their subsequent evaluation of the websites could in the order of two months. Adding in time to organise and analyse the data produced, to write it up and have it reviewed by project supervisors and other stakeholders, it is a realistic estimate that this could take up to four months to complete. If additional websites were also to be assessed, adding, for example, the next twenty applicable websites, this would effectively double the time required for the raters to perform the assessments. Moreover, the two original raters would also have to assess these additional websites. Given the increased workload and the enlarged dataset that would be produced – completion of the work, in this case, could take in excess of six months.

**ii) Number of Websites Rated**

The rationale for using the first page of a Google search was explained in the text of the chapters 6 and 7 (new chapters 7 and 8) and was based on independently published reports describing how searchers typically access only those sites on the first page of a search result without advancing beyond to the second page (in fact, research shows that many searchers do not go beyond the first three search results - on the top half of the first page). Furthermore, several publications report methods that attempt to best mimic what a patient searching for information online is most likely to look at, for
example: [8, 9, 14, 17]. As this was a stated goal of the study, and given that the scope was clearly described, as were all inclusions and exclusions of websites assessed, the number of websites utilised can be defended and scientifically supported.

The assessment of additional generic medicines websites may not develop the WQA tool further or add to its robustness. Importantly, research has suggested that use of search results from further down results lists may be of no benefit as they are often likely to be duplications of earlier results [18]. Moreover, given the time that has elapsed since this study was originally performed (2 years), it would be difficult to validly add to the original dataset.

While it was not anticipated that the WQA tool developed for this thesis would be used to assess topics other than generic medicines, it would be possible, in terms of future research (and as described in the JMIR paper), to adopt the principle of the WQA tool for use in assessment of online information in other subject areas. This would require subject matter experts in such areas to develop the necessary questions to be asked to assess information on other topics. Moreover, the specific search terms would also have to be identified for Internet searches which would be required to find the websites to be investigated; decisions regarding these terms would also require expert input.

**Conclusion**

The development of the WQA tool, and its implementation, have been extensively reviewed by independent experts in the field of medical internet research and related software/tools and was subsequently published [19, 20]. The methodology used is similar to analogous tools developed in this field for assessment of different subject
areas. The tool has been shown to be reproducible between two reviewers which is the approach taken for other previously published tools.

Future research could adopt the principle of the WQA tool for use in other areas of assessment of online information and greater numbers of raters could be used to add to what is already known about the robustness of this tool. As the tool would need to be revised to reflect a different subject area, this would require the input of subject matter experts in those areas, and would make an interesting area for future investigation.

The development of the WQA tool for use in other areas is, however, outside the scope of this thesis.
References


Addendum 2 to Chapter 8

Objective

The objective of this addendum is to use the work completed with the WQA tool in the design of a fictional website, the aim of which would be to provide information to the general public on what generic medicines are.

This addendum will also describe a plan for potential evaluation of such a website to ensure that it meets its stated objectives.
Part 1 – Website Design and Content

Website title:
What Are Generic Medicines?

Definition of Purpose:
The goal of this website is to provide accurate and understandable information about
generic medicines to members of the general public, explaining what generic medicines
are and how they are similar to, and differ from, brand-name medicines.

Scope:
Applies to general description and information in relation to the topic of generic
medicines (as was assessed by the WQA tool).
Excludes clinical information such as specific information about activity or effects of
drugs.

Target audience:
General public. The aim is provision of information to patients or members of the
general public, without specific scientific or medical training or education, who are
seeking information on what generic medicines are.

Format:
The website would be formatted as a non-complex “Frequently Asked Questions” (FAQ)
type structure.
A series of questions, based on the WQA tool, would be presented to the user. Clicking on the question would show the appropriate answer.

Questions and answers would be written to be readable and understandable to the majority of members of the general public, as explained below.

**Content Plan:**

1. Home page content.
2. FAQs & Answers – based on WQA analyses [1].
3. Use of “rollovers/mouseovers” to provide definitions of words, where necessary, and improve “interactiveness” of the website.
4. Ensure text is appropriate as per Flesch Reading Ease and Flesch-Kinkaid Grade Level indicators.
5. Additional suggestions based on WQA analyses.

**Specific Content**

1. The home page would contain a definition of generic medicine:

What is a generic medicine?

Generic medicines are safe copies of well-known medicines. They contain the same active ingredient as the product they are based on, and they're just as effective and just as safe as branded medicines.

Information would also be provided to users explaining that this is a Frequently Asked Questions (FAQs) website, providing information about what generic medicines are.
Information would be provided to users that clicking on any of the FAQs would bring up the answer to that question.

A link to the HSE website page “Questions about Generic” should also be included (http://www.hse.ie/eng/health/hl/Generics/questions/).

2. Based on the WQA analyses, the following FAQs and answers would be presented to users.

3. Rollover definitions, where to be used, are indicted by an asterisk (*) after the word to be defined.

<table>
<thead>
<tr>
<th>No.</th>
<th>Question</th>
<th>Answer</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>What exactly is a generic medicine?</td>
<td>New medicines are protected by patents* for a number of years. This means that only the patent holder is allowed to make the medicine. After the patent runs out, other companies are then able to make this medicine. The copies made by these other companies are called “generic medicines”.</td>
</tr>
</tbody>
</table>

*Rollover definition for “patent”: A patent is a licence that gives sole permission only to the person or company holding the patent, to make or sell a product. Patents apply for a set
<table>
<thead>
<tr>
<th>No.</th>
<th>Question</th>
<th>Answer</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>period of time.</td>
</tr>
<tr>
<td>2.</td>
<td>Are generic medicines exactly the same as brand name medicines?</td>
<td>Generic medicines contain the same active ingredient and have the same dose and strength. They are taken in the same way. They are just as safe and effective. They are used to treat the same illness as the brand name medicine.</td>
</tr>
<tr>
<td>3.</td>
<td>What are the differences between generic medicines and brand name medicines?</td>
<td>Equivalent* generic medicines can have a different appearance. They might be different in colour, size or shape. They might have a different taste or smell. Generic medicines will have a different name to the brand name. Generic medicines have the same active ingredient but the other ingredients in the medicine, like colours or flavours, can be different.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>*Rollover definition for “equivalent”: Equal to the brand name medicine.</td>
</tr>
<tr>
<td>4.</td>
<td>What are some examples of generic medicines?</td>
<td>Generic medicines are not allowed to use the brand name. They are usually known by the name of the active ingredient in the medicine.</td>
</tr>
<tr>
<td>No.</td>
<td>Question</td>
<td>Answer</td>
</tr>
<tr>
<td>-----</td>
<td>---------------------------------------------</td>
<td>-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Some well known branded medicines have generic versions, for example:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>The generic form of Lipitor™ is called atorvastatin.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Valium™ is also known as diazepam.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Viagra™ is also known as sildenafil.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Rollover definitions:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>*Lipitor™/atorvastatin is a medicine used to lower cholesterol.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>*Valium™/diazepam is a medicine used to treat anxiety.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>*Viagra™/sildenafil is a medicine to treat erectile dysfunction.</td>
</tr>
<tr>
<td>5.</td>
<td>What is bioequivalence?</td>
<td>Bioequivalence, also called BE, is testing that is done on a generic copy of a medicine. This is used to show that it is equal to the brand name medicine in how it becomes available for use in your body.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>BE testing must be done on all generic medicines to allow them to be available for you to buy.</td>
</tr>
<tr>
<td>6.</td>
<td>Why are generic medicines often less expensive than brand name</td>
<td>When a patent* runs out other companies can now make copies of the</td>
</tr>
<tr>
<td>No.</td>
<td>Question</td>
<td>Answer</td>
</tr>
<tr>
<td>-----</td>
<td>----------</td>
<td>--------</td>
</tr>
<tr>
<td></td>
<td>medicines?</td>
<td>medicine. This means that there is competition, and so the price drops. Also, the makers of the generic medicine do not invent the medicine. They are making a copy. That means that they do not have any of the costs for inventing a new medicine. This means that they can make it for a lower price.</td>
</tr>
<tr>
<td>7.</td>
<td>Why should I choose a generic medicine?</td>
<td>You get the same medicine for a lower price. The lower priced medicine is just as safe and effective as the brand name medicine.</td>
</tr>
<tr>
<td>8.</td>
<td>Are there any reasons why I shouldn’t choose a generic medicine?</td>
<td>In most cases a generic medicine will work just as well as the brand name medicine. Sometimes doctors prefer not to use generics for some illnesses. Your doctor will tell you about this and answer any questions. If you have ever had an allergy to a medicine, tell your pharmacist or doctor. This is because some</td>
</tr>
<tr>
<td>No.</td>
<td>Question</td>
<td>Answer</td>
</tr>
<tr>
<td>-----</td>
<td>-------------------------------------------------------------------------</td>
<td>----------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td></td>
<td>ingredients can be different in a generic medicine.</td>
<td></td>
</tr>
<tr>
<td>9.</td>
<td>How much money could I save using generic medicines?</td>
<td>Generic medicines are often about a third cheaper. Sometimes there isn’t any difference. Be sure to check with your pharmacist.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>For example: in October 2010 a generic version of a medicine to treat high cholesterol cost £1.12 for a pack of 28, in the UK. This compared to about £30 for a pack of 28 of the brand name medicine [2].</td>
</tr>
<tr>
<td>10.</td>
<td>Are there generic versions of all brand name medicines?</td>
<td>No. It is only after the patent* expires that a generic copy of a medicine can be made. New medicines that are still under patent will not have generic versions.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>*defined previously.</td>
</tr>
<tr>
<td>11.</td>
<td>What are Narrow Therapeutic Index (NTI) medicines?</td>
<td>These are medicines where the amount of the medicine that will treat an illness is very close to the amount that could be bad for you.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Doctors monitor people who are taking</td>
</tr>
<tr>
<td>No.</td>
<td>Question</td>
<td>Answer</td>
</tr>
<tr>
<td>-----</td>
<td>---------------------------------------------------</td>
<td>----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td></td>
<td>These medicines very closely. This is done to be</td>
<td>sure that they are getting the right amount. Examples of NTI medicines are: lithium and warfarin. If you are unsure about the medicine you are taking, ask your doctor or pharmacist for advice.</td>
</tr>
<tr>
<td>12</td>
<td>Why do generic medicines have different names?</td>
<td>The makers of generic medicines are not allowed to use the brand name. This is because it is a trademark*. Generics are usually known by the name of the active ingredient in the medicine. The brand name is also called the proprietary name. This means that the name is owned by the company that invented the medicine. Examples of proprietary names are Lipitor™ and Viagra™. The active ingredient in every medicine has its own name – this is called the “International Non-proprietary Name” or INN. This means that no one owns this name, and everyone can use this</td>
</tr>
</tbody>
</table>

*Trademark: A trademark is a word, phrase, symbol, or design that is used to distinguish one company's products or services from another. It is a type of intellectual property that can be legally protected. In the context of the passage, the brand name is a registered trademark of the company that invented the medication. Trademark protection can prevent others from using the brand name to sell similar products, ensuring consumers can identify the company's brand consistently. The term “proprietary” refers to something owned by the company, distinguishing it from the active ingredient’s INN, which is universally recognized and available for all to use.
<table>
<thead>
<tr>
<th>No.</th>
<th>Question</th>
<th>Answer</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td><strong>name. Generic medicines are often known by this name.</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>See the question: “What are some examples of generic medicines?” for more information.</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Rollover definition:</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>A trademark is a symbol or word that represents a company or product and can only be used by the person or company who owns it. It is denoted using the symbol ™.</em></td>
</tr>
<tr>
<td>13.</td>
<td>What is generic prescribing?</td>
<td>When a doctor writes a prescription they can write down either the brand name or the generic name of the medicine.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>If the doctor writes the generic name this is known as “generic prescribing”.</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>See question: “Why do generic medicines have different names?” for more on the INN.</strong></td>
</tr>
</tbody>
</table>
4. Ensure text is appropriate as per Flesch Reading Ease and Flesch-Kinkaid Grade Level indicators.

According to published literature (and as used during WQA evaluations), a minimum score of 60 for Flesch Reading Ease, and a maximum score of 8 for Flesch-Kincaid Grade Level, is recommended for ease of reading [3].

A sample of each answer to the FAQs was analysed to see if it met with these requirements. Scores achieved were:

<table>
<thead>
<tr>
<th>Answer number</th>
<th>Flesch Reading Ease Score</th>
<th>Flesch-Kincaid Grade Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>62.1</td>
<td>7.7</td>
</tr>
<tr>
<td>2.</td>
<td>82.9</td>
<td>4.2</td>
</tr>
<tr>
<td>3.</td>
<td>63.1</td>
<td>7.4</td>
</tr>
<tr>
<td>4.</td>
<td>67.7</td>
<td>6.7</td>
</tr>
<tr>
<td>5.</td>
<td>62.1</td>
<td>9.4</td>
</tr>
<tr>
<td>6.</td>
<td>77.4</td>
<td>5.3</td>
</tr>
<tr>
<td>7.</td>
<td>74.8</td>
<td>5.8</td>
</tr>
<tr>
<td>8.</td>
<td>63.9</td>
<td>7.3</td>
</tr>
<tr>
<td>9.</td>
<td>56.2</td>
<td>7.0</td>
</tr>
<tr>
<td>10.</td>
<td>66.9</td>
<td>6.4</td>
</tr>
<tr>
<td>11.</td>
<td>72.8</td>
<td>7.1</td>
</tr>
<tr>
<td>12.</td>
<td>68.0</td>
<td>6.4</td>
</tr>
<tr>
<td>13.</td>
<td>67.6</td>
<td>8.0</td>
</tr>
</tbody>
</table>
5. Additional suggestions

Based on results from WQA analyses of websites (and on other research in this thesis), the following additional suggestions are made for the design and content of this website:

a. A profile, or information about the author, including their qualifications and experience should be included. This allows users to see that the content was prepared by a person with suitable education and experience and will thereby increase their trust in the information provided.

b. Provide explanation of any terms that could be easily confused e.g. “generic” and “genetic”.

c. Advertising should not be allowed on the site as it detracts from the message and may be a source of confusion for the user.
Part 2 – Website Evaluation

Evaluation of website to ensure it achieves its goals, as stated above.
To be evaluated:
1. Information provided.
2. Readability.

Methods of evaluation:
1. WQA tool – assessment of both content and readability [3].
2. Other evaluations.

1. WQA analysis
Using the established assessment methodology for the WQA tool developed as part of this thesis, a score of 22 (the maximum possible score) would be achieved based on the content in the FAQs described previously.

Furthermore, analysis of the readability of the answers provided shows that all answers are in the recommended category for Flesch-Kinkaid Grade Level, having a maximum score of 8.0. All answers with the exception of answer 9 have the recommended Flesch Reading Ease score of greater than 60. Response number 9 is a little more complex than many of the other answers provided, as it includes an example of cost differentials.

Further action, as described later, could be taken during the evaluation stage to try to mitigate this issue.
2. Other evaluations:

Evaluations of medical information-providing websites have been described in the literature in relation to many different areas of focus. Techniques could be adopted from the literature for evaluation, which include, but are not limited to:

- **Assessment of the extent to which users were better educated about generic medicines after visiting the website**, in a manner similar to that described by Chen *et al* [4]. The Chen *et al* study involved taking data from a previously completed survey (in this case, relating to colorectal cancer screening) and evaluating the effects of Internet-provided health information on patient behaviour (compliance with colorectal cancer screening). In the context of the website being discussed here, a different approach would have to be taken as there is no pre-existing data source. The Chen study approach could be adapted to survey patients’ understanding of generic medicines pre- and post-accessing the website. Comparing levels of understanding before and after interacting with the website would provide knowledge on the impact the information provided has had on users’ understanding of generic medicines, and how this changed due to the information provided. Levels of consumer confidence in generic medicines could also be assessed, alongside understanding, to investigate if an improvement in understanding of what generic medicines are correlates in any way with improved consumer confidence in generic medicines (this is especially pertinent as consumer confidence in generic medicines has been shown to be poor [5]). The survey provided in section 3 could be used as both the pre- and post-assessment tool, and could be adapted to include questions
relating to consumer confidence, as stated.

- **Assessment of usability of the website** in a manner similar to that described by Janiak *et al* [6]. Such an evaluation would firstly assess the literacy demands of the written content using the Suitability Assessment of Materials (SAM) instrument[7]. The SAM rates materials on 22 factors to evaluate the following: (1) content, (2) literacy demand, (3) graphics, (4) layout and typography, (5) learning stimulation and motivation, and (6) cultural appropriateness.

Secondly, the usability of the website would be evaluated to determine if users can effectively and efficiently use the site. This evaluation could be completed by performing usability interviews with users. However, in the case where interviews with users might not be possible, an alternative written survey evaluation method has also been provided in part 3.

3. User Surveys

Users arriving at the website could be invited, using a “pop-up box” to complete a survey. To encourage users to participate the invitation should state that the survey is quick and simple and will not take more than five minutes of their time. Results could be forwarded to website authors and analysed to determine user opinions and also used to make improvements to the content.

Sample survey is provided below:

<table>
<thead>
<tr>
<th>Survey Question</th>
<th>Response</th>
</tr>
</thead>
</table>
| i. How easy did you find the website to use | □ Very easy  
  □ Easy |
<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>ii.</td>
<td>Did you find the information you were looking for?</td>
</tr>
<tr>
<td>iii.</td>
<td>How understandable was the information provided?</td>
</tr>
<tr>
<td>iv.</td>
<td>How satisfied were you that this website provided the information you needed about generic medicines?</td>
</tr>
<tr>
<td>v.</td>
<td>Was there any information you were looking for that was not provided?</td>
</tr>
<tr>
<td>vi.</td>
<td>If yes, what information was that:</td>
</tr>
<tr>
<td>vii.</td>
<td>Did you have any questions that were not in the FAQs?</td>
</tr>
<tr>
<td>viii.</td>
<td>If yes, what questions:</td>
</tr>
<tr>
<td>ix.</td>
<td>How easy was it to find what you were looking for?</td>
</tr>
<tr>
<td>x.</td>
<td>Overall, how satisfied were you with the website?</td>
</tr>
</tbody>
</table>
xi. What content would you like to see added?

xii. What other suggestions would you have for improvement?

xiii. Has this website changed your view of generic medicines?  □ Yes  □ No

Please explain your answer:

Where consumer confidence in generics is to be assessed, add the following:

xiv. How do you feel about taking a generic medicine?  □ I would be happy to take a generic medicine.  □ I would prefer not to take a generic medicine.

Conclusion

Information from any or all of the evaluation methods described above may be used on an on-going basis to make iterative improvements to the content and user-friendliness of the website. For example, it can be seen from the initial structure of the FAQs that there is already scope to improve the answers to many of the answers, particularly the answer to question 9. Specific user-based focus groups or surveys could also be used to help to determine appropriate wording. The input of experts in preparation of medical
material for the general public could also be made use of in the areas identified by these evaluation methods.

Furthermore, analysis of the success of internet-based interventions (as discussed by Bennett and Glasgow [8]) for the delivery of healthcare related information, recommend engagement with Web 2.0 features – such as social networking – to ensure on-going engagement and prevention of attrition of users over time. Integrating this website with Web 2.0 functionality, along with the discussed on-going evaluation and user input could ensure that such a website would be the “go to” site for consumers of medicines, in Ireland and possibly internationally, who are searching for an answer to the question: “what exactly is a generic medicine?”
References


Chapter 9

Generic medicines: an evaluation of the accuracy and accessibility of information available on the Internet.

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Citation:


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Generic medicines: an evaluation of the accuracy and accessibility of information available on the Internet

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Abstract

Background
Internationally, generic medicines are increasingly seen as a key strategy to reduce healthcare expenditure, therefore awareness and knowledge transfer on this topic is a priority. Although the Internet is a frequently used source of medical information, the accuracy of material found online is variable. The aim of this study was to evaluate information provided on the Internet regarding generic medicines in terms of both quality of information and accessibility (in terms of readability).

Methods
Internet searches were completed, with a pre-defined search term, using the Google search engine, in five English-speaking geographical regions (US, UK, Ireland, Canada and Australia). Search results likely to be looked at by a searcher were collated and assessed for the quality of information in the websites, using a newly developed Website Quality Assessment (WQA) tool; and for readability, using existing methods. The reproducibility of the tools between two independent reviewers was evaluated and correlations between WQA score, readability statistics and Google search engine results page (SERP) ranking were assessed.

Results
Wikipedia was the highest-ranking search result in 100% of searches performed. Considerable variability of search results returned between different geographical regions was observed, including that websites identified in the Australian search generated the highest number of country specific websites; searches performed using computers with Irish, British, American and Canadian IP addresses appear to be more similar to each other than the google.com search performed in Australia; and the
Canadian google.ca results show a notable difference from any of the other searches. Of the 24 websites assessed, none scored a perfect WQA score. Notably, strong correlation was seen between WQA and readability scores and ranking on google.com search results.

Conclusions

This novel evaluation of websites providing information on generic medicines showed that, of the websites likely to be seen by a searcher, none demonstrated a combination of scoring highly on quality of information (as evinced by WQA score) and readability. Therefore, there is a gap in online knowledge provision on this topic which, if filled by a website designed using the WQA tool developed in this study, is likely to rank highly in google.com SERPs.

Keywords

Generic medicine, Internet, medical information, patient education, Google, readability.
Background

The Internet has become a source of medical information for patients and healthcare professionals alike. However, the accuracy of information found online may not always necessarily be relied on, and concerns have been raised about the quality of information that may be found, by patients, on the Internet [1-4]. In an era when healthcare costs are soaring, many governments around the world are increasingly making use of generic medicines to help constrain expenditure. Additionally, many commonly used proprietary medicines have recently, or will in the near future, hit the so-called “patent cliff” – thus opening them up to generic competition [5-7]. As a result of this, patients are increasingly likely to be prescribed generic medicines, possibly in place of a more familiar proprietary brand. When a patient has medical or healthcare queries, such as questions about generic medicines, the Internet is likely to be one of the first places they will try to find information [8]. Therefore, the question should be asked: Is the information available on the Internet regarding generic medicines accurate, accessible and of good quality? (Please note: for the purposes of this study, the term “accessibility” is used in the context of accessibility of the information provided – that is: how readable and understandable is the information provided, to the lay reader).

A multitude of studies have assessed the use, quality and/or availability of medical/healthcare information available on the Internet in areas as diverse as: inflammatory bowel disease [9], orthodontistry [10, 11], pain [12], cancer [13-15], and mental health [16, 17], amongst many others. Such studies often look at information available to, and used by, people in particular geographic areas, for example: paediatric asthma in Saudi Arabia [18], preconception care in Italy [19], and medical information in Brazil [20] and Portugal [21]. As many misconceptions exist about generic medicines, and given that healthcare professionals have expressed poor opinions of generics in the
past [22], there is a challenge in ensuring that accurate and relevant information is communicated to the general public. This challenge includes not only the necessity to provide accurate information, to dispel myths and to counter misinformation, but also to present the material in a manner that is accessible to the intended audience. It has been reported that, in the case of patients particularly, there is a feeling that myths and questions remain about generic medicines, and that accurate information can be difficult to source [23].

The aim of this study was to evaluate the availability of information on the Internet regarding generic medicines. This study additionally assessed whether the information in the websites likely to be looked at by patients is accurate (as measured by WQA) and accessible (as measured by readability statistics). While a plethora of information exists on research into the provision of medical information on the Internet in many and varying areas, to the authors’ knowledge, no evaluation has been published specifically on the quality and accessibility of information on generic medicines. This study aimed to bridge that knowledge gap while also evaluating availability and accessibility of that information in several English-speaking countries.
Methods

Choice of Search Engine
StatCounter, a web analytics company, reports in their “GlobalStats graph” that for the 12 month period from Jan 2012 to Jan 2013 - Google was the most commonly used search engine globally, holding approximately 90% of the worldwide search engine market [24]. Therefore, as Google is the search engine of choice globally, Google was the search engine used for this study.

Choice of Search Term
A patient wishing to make an Internet enquiry about a generic medicine is likely to use either the term “generic drug”, or “generic medicine” as their search term. To accommodate both of these terms, the search term used for this study was “generic medicine OR drug” (without the quotation marks, and with the “OR” capitalised).

The reasoning for this is that Google's default behaviour is to consider all the words in a search. In order to allow either of the words “drug” or “medicine” to be searched for, the “OR” operator can be used (the OR must be in capitals). With this search, Google will return SERP hits that contain the word “generic” and either of the words “drug” or “medicine”. Without the “OR” operator, Google would only return SERP pages that have both the words “drug” and “medicine” on the page, as the “AND” operator is the default [25].

All searches were performed during March and April of 2012.

Inclusion of Web Sites
A study from 2008 showed that 68% of search engine users click a search result within the first page of results (the default for Google is 10 results per page), and are unlikely
to go to the second page of search results [26]. Therefore, following a search using the identified search term, the results on the first SERP returned, that meet the following inclusion criteria, were assessed: (i) web site is written in English; (ii) web site is not a portal serving to provide links to third party sites; (iii) web site is not a news story (e.g., as found by the Google news search); (iv) web site is not a sales website and (v) website is not spurious and is related to the topic of generic medicines.

**Determination of Global Variability**

To assess global variability, searches were performed in regional Google search engines, google.ie (Ireland), google.co.uk (United Kingdom), google.ca (Canada), and google.com.au (Australia) in addition to the main US site: google.com.

In order to assess if Internet Protocol (IP) addresses have any impact on the results obtained, the search was also performed using google.com, on computers in the following five regions: Ireland, United States, Great Britain, Australia, and Canada.

IP stands for “Internet Protocol”. Every device (e.g., computer, tablet, printer etc.) on a computer network has a unique, numeric identifier called an IP address. Similarly to how someone sending a letter would write the intended address on the envelope, a computer’s IP address is used to identify and locate that specific device on a computer network, or on the Internet [27].

Overall, two searches (that is: on the local and .com sites) were performed on computers with an IP address in each of the five regions above, meaning that a total of nine searches were completed.
Assessment of Quality of Information

The questions in Table 1 – Website Quality Assessment (WQA) Questions for Website Information were asked in relation to each website. The WQA tool was developed for this study as, to the best of the authors’ knowledge, no previous assessment of websites providing information about generic medicines had been performed. The WQA tool consists of 22 yes/no type questions, where a point is awarded for positive or correct information. No points are awarded where information was lacking, or for inaccurate information. Questions that could not be answered were designated “not applicable” (N/A) and no score awarded. An overall WQA score for each website was totalled from the scores given to each assessment question. (In some cases just the initial page linked to in the Google search was assessed; however, in the case where clear and relevant links to other pages containing information of interest within the same website were obvious to the searcher, these were also included in the assessment).

The questions in the WQA were designed to account for all of the information that a patient might need in order to accurately answer any questions they may have about generic drugs, for example: an explanation as to what a generic drug is and how it differs from a proprietary drug – including price, appearance etc.; explanation of bioequivalence; examples of generic drugs and their proprietary counterparts; information regarding when generic substitution may not be appropriate – e.g., in the case of narrow therapeutic index drugs and any pros or cons of generic medicines.

Assessment of Website Readability

A minimum of a 100-word sample of continuous text from each of the websites was extracted and pasted into Microsoft Word. This text was then analysed using the Flesch Reading Ease score [28] in the MS Word application.
MS Word’s Flesch Reading Ease score is based on a formula developed in 1948 by Rudolf Flesch [28]. It is computed using the average number of syllables per word and words per sentence. Syllables-per-word is a measure of word difficulty. Words-per-sentence is an indicator of syntactic complexity.

The Flesch Reading Ease scale ranges from zero to 100. Zero to 50 is very difficult to difficult reading. Eighty and above is easy to very easy reading. Flesch himself set the minimum score for plain English at 60 [28]. Microsoft’s documentation encourages authors of standard documents to aim for a score of 60 to 70 [29, 30].

Additionally, the Flesch-Kincaid Grade Level was used to determine the readability score for each website. The Flesch-Kincaid Grade Level, which was developed in 1975, measures the readability of a document based on the minimum education level required for a reader to understand it [31]. Microsoft recommends aiming for a Flesch-Kincaid score of 7.0 to 8.0 for most documents. According to a 1993 study, the average adult in the U.S. reads at the seventh-grade level and the authors of that study recommended that materials for the public be written at a fifth- or sixth-grade reading level [29].

**Statistical Analyses**

Two reviewers rated each selected website independently and their scores were compared to assess reproducibility of the WQA tool and the readability assessments. The intraclass correlation coefficient (ICC) was used to measure reproducibility. Spearman’s correlation coefficient was used to measure the association between the ranking of websites with WQA scores and readability assessments. The scores from the developer of the assessment tool (SD) were used in the correlation analyses. The
correlation between ranking of websites and WQA scores was also used to demonstrate the predictive validity of this newly developed assessment tool.
Results

Determination of Websites for Assessment

Thirty-eight (38) unique hits (i.e. individual search results) were identified from the first SERPs of the nine searches performed. Of these, 15 hits were discarded for the reasons described in the methodology or were amalgamated with another hit. (For example, the website entitled: EGA - Basics of generic medicines was a hit on both of the IE searches. Additionally, the main EGA website was a hit on the google.co.uk search. As both relate to the same website, the results were combined into one and the EGA website assessed as a single site, rather than individual pages).

An additional website – entitled Generics Are The Same - was added during the rating exercise as it was directly referred to in the Canadian Generic Pharmaceutical Association website and is also published by the Canadian Generic Pharmaceutical Association. As the Generics Are The Same website is the explanatory arm of the Canadian Generic Pharmaceutical Association website it was decided to also assess this website as a patient accessing the first website is very likely to follow links through to the second. This was the only example of an associated website being assessed.

Overall, a total of 24 individual websites were assessed using the Website Quality Assessment tool. Results of the assessments for each of the 24 websites are displayed in Table 2, which additionally shows the ranking on the Google search results page for each website assessed, in each of the individual domain searches.

Analysis of Websites from Search Results

Visual analysis of the search results (Table 2), including comparison of the international searches, shows that Wikipedia (a collaboratively edited, multilingual,
free Internet encyclopedia supported by the non-profit Wikimedia Foundation) was the number one ranked search result in 100% of the searches completed. This is consistent with findings in other studies [32, 33]. Wikipedia is the 6th most accessed website on the Internet globally [34] and both this fact, and the results from this study, show that Wikipedia is highly likely to be visited by online information seekers, including those seeking medical information.

After Wikipedia, the following five websites were the most likely to be used by searchers, based on the search terms used in this study:

- About.com’s page entitled *Generic Drugs: Know the Benefits and Differences of Generic Drugs*
- MedicineNet.com’s page: *Generic Drugs, Are They as Good as Brand Names?*
- The US Food and Drug Administration (FDA)’s page entitled *Understanding Generic Drugs*
- NetDoctor.co.uk’s page entitled *Branded and generic medicines*
- The World Health Organisation’s page: *Generic Drugs*

These six websites (Wikipedia and the five others above that appear most often) all appear in at least six of the nine searches completed (Table 2).

SERPs returned to searchers during this study demonstrate that a search, using identical search terms, performed in the local Google search engine, compared to that performed on the same computer (i.e., same IP address) but in the google.com domain, can provide substantially different results (Table 2). Other notable observations from Table 2 include that the European Generic Medicines Association (EGA) website was a hit in three of the four searches conducted in Europe (it was not a result in the google.com UK search) but was not seen in any of the other searches. This could indicate a possible regional variance. However, the FDA website (an American website)
was a hit in all searches, with the exception of the Canadian google.ca search (it was a hit in the Canadian google.com search). This could be due to the fact that FDA is the US pharmaceutical regulator and a highly used, recognised and reputable resource worldwide. Additionally, it was noted that the websites returned from the Australian searches had the highest level of country/domain specific websites with six unique website hits being seen between the Australian google.com and google.com.au searches that are not seen elsewhere.

The google.com searches performed using computers with Irish, British, American and Canadian IP addresses appear to be more similar to each other than the google.com search performed in Australia. The Australian google.com profile is noticeably different from the other search results with two unique websites not seen in any of the other google.com searches.

Interestingly, the Canadian google.ca results show a notable difference from any of the other searches due to the absence of most of the websites seen in other regional searches, with the exception of Wikipedia and Canadian websites.

Some of the geographical regions in Table 2 do not have the full list of top 10 websites identified in the search as some websites were discarded as described in the methodology.
WQA Scores

The WQA tool (Table 1) employed the use of 22 yes/no type questions to assess the quality of information contained in each website. From a maximum available score of 22, the highest score awarded during the rating exercise was 17 - awarded to two websites: (i) Netdoctor.co.uk – *Branded and generic medicines* and (ii) The Irish National Information Centre’s publication - *Generic Prescribing* (websites numbered 5 and 9 respectively in Table 3). However, only one of these two websites was in the top six sites indicated by the Google search rankings and as described above – the Netdoctor.co.uk site. The Irish National Information Centre’s publication was a result only in the google.ie (Irish IP address) search, which means its likelihood of being seen outside Ireland is small.

WQA scores of 16 (the second highest WQA score awarded) were given to three websites: (i) Wikipedia’s *Generic drug* page, the highest ranking website by Google search result, (ii) About.com’s page entitled *Generic Drugs: Know the Benefits and Differences of Generic Drugs* and (iii) the FDA’s *Understanding Generic Drugs* (websites numbered 1, 2, and 4 respectively in Table 3). All three websites were situated in the top six websites most observed in the Google SERPs obtained.

The remaining two sites seen in the top six most highly hit websites scored WQA scores of 11 (MedicineNet page, website number 3 in Table 3) and 10 (WHO page, website number 6 in Table 3), indicating that the extent and quality of information in these websites is less than the other four top hits, and considerably lower than some of the other websites assessed in this study. This indicates that not all of the websites that are the most likely to be seen by searchers contain the best or most accurate information on generic medicines.
WQA scores of 15 were awarded to two other websites, indicating relatively good information content. These are (i) *Generic Drugs - What are Generic Drugs?* (number 10 in Table 3) and (ii) Australian Prescriber: *Frequently asked questions about generic medicines* (number 21, Table 3). These websites were each hits on one search only - the Irish google.ie and Australian google.com.au searches, respectively. This indicates that only searchers in Ireland and Australia would be likely to find and read this content.

The association between WQA score and ranking in the Google search results was investigated and a moderate to strong correlation (defined as an absolute value of Spearman’s correlation coefficient $> 0.3$) was found for searches done in the google.com domain (Figure 1 and Table 4). The most commonly identified websites, i.e., ranked 1, 2 etc., tended to have higher WQA scores. While a moderate to strong correlation was found in the .com searches, it was not seen in the local (that is: google.ie/.co.uk/.ca and .com.au) searches, with no correlation between WQA scores and ranking being observed in the .ie and .com.au searches.

**Readability scores**

A Flesch Reading Ease score of 60 or greater and a Flesch Kincaid Grade Level of less than 8 are recommended for general ease of reading.

Three of the websites assessed had a Reading Ease score of greater than or equal to 60: (i) Rx List – Facts about Generic Drugs, (ii) Generic Drugs – The same Medicine for Less Money and (iii) Generic vs. Brand Name Medicines (numbered 7, 19, and 13 respectively, in Table 3).

Five of the assessed websites had Grade Level scores of 8 or less: (i) RxList – Facts About Generic Drugs, (ii) Generic Drugs – The Same Medicine for Less Money, (iii)
Benefiting from Generic Drug Competition in Canada: The Way Forward, (iv) Generic vs. Brand Name Medicines, and (v) Generic Drugs: Know the Benefits and Differences of Generic Drugs – about.com (numbered 7, 19, 18, 13, and 2 respectively, in Table 3).

Therefore, as the three websites with the best Reading Ease scores also feature in the list with the appropriate Grade Level scores, it can be determined that those three websites (numbered 7, 19 and 13, respectively, in table 3) were the easiest for a member of the public, without a scientific background, to read and understand. As these three websites scored relatively low on assessment of the quality of the information they contained - with WQA scores of 9, 10, and 9 respectively (Figure 2) – this study did not have an opportunity to assess a site with good readability statistics and containing good quality information. However, analogously to what was demonstrated for WQA scores, Reading Ease scores also demonstrate a relationship with ranking on Google searches. Results from this study indicate that easier to read websites rank higher in Google.com search rankings (Figure 1 and Table 4). Finding statistically significant correlations was limited by the small sample sizes (at most 10 for the top 10 websites in each domain) but a statistically significant correlation was found for the US google.com search ($r_s=-0.64, p=0.048$). The scores for the Flesch Kincaid Grade Level have also been correlated with ranking of the websites on all domains (Figure 1 and Table 4). In general, the top ranked sites tend to have lower Grade Level values.

**Reproducibility**

Comparison of the scores of the two independent reviewers (SD and NC) show that, for WQA assessments of the websites, almost perfect agreement was seen on average (ICC = 0.94). Similar analysis of the readability of the websites using Flesch Reading Ease
score and Flesch-Kincaid Grade Level showed moderate to strong levels of agreement between the two reviewers. (ICC value = 0.71 and 0.63 respectively).

Readability scores were assessed by taking a section of text from the website and calculating readability statistics using MS Word. As each rating was independent, different sections of text were likely to be taken from each of the websites assessed. This variation in the text taken is likely to account for the lower levels of agreement for the reading assessments, compared to the WQA tool. Given the subjectivity of this type of readability assessment, and the possible variability in the text selected by reviewers for assessment, it is reasonable to state that a moderate consistency in the writing throughout the websites assessed was observed.

Overall the WQA and readability scores demonstrate acceptable reproducibility between two reviewers.
Conclusions

This study is novel in that it is the first to assess the websites most likely to be read by a patient searching the Internet for information about generic medicines. More specifically, using the WQA tool developed in this study, we determined that these websites were all lacking at least some of the information that the authors considered appropriate and relevant to the topic of generics. However, it is noteworthy that none of the websites appeared to contain purposefully inaccurate information (as determined by the WQA tool’s questions); rather they did not contain information that was considered important and that would have gained the website a higher WQA score in our assessments.

Despite known shortcomings and criticisms [35, 36], which include bias, and the potential ability for the information it contains to be corrupted; use of Wikipedia, as a primary source of information, is prevalent worldwide. Wikipedia is currently the sixth most accessed website globally [34], whereas it was the eighth most accessed during a study completed in 2009 [33]. With clinicians as well as medical students increasingly using Wikipedia as a source of information [35] (with ease of access and ease of understanding being the main reasons cited for its usage amongst medical students), [37] it is reasonable to expect that this resource will also be one of the first stops for patients searching for medical information. Recognition of Wikipedia’s prevalence has sparked debate as to whether clinicians should engage with editing Wikipedia to help provide accurate information to patients [38, 39]. As the results of this study indicate that no matter where in the world a patient may search for information on generic medicines they are likely to find Wikipedia as the first result (Table 2), the question should be asked if there is an onus on governments or government-provided healthcare systems to engage with editing of Wikipedia in order to ensure that the information
contained therein is impartial as well as accurate. Indeed, given the prevalence of use of internet information and social networking associated with “web 2.0” [40], this is an area which is likely to increase in importance in the future.

Looking at the other five websites which were most likely to be accessed by a searcher (see Table 2), about.com is a resource website containing articles and other information which are organized into “channels” on various topics. Freelance writers, referred to as “Guides”, author the articles. About.com differs from Wikipedia in that it is not open to editing by anyone, and that it makes use of advertising. The about.com website pages assessed in this study were written by a “patient empowerment guide” who, according to information on the website, did not have a scientific or medical background. In addition, this website appeared to contain quite a high amount of advertising which was placed in very close proximity to the article information, making it possible for the searcher to confuse the actual information provided with the advertising content. The MedicineNet website contained similar levels of advertising to those seen in about.com. However, the author and editor of this page held an MD and PhD, respectively, which may give it more weight in a searcher’s opinion. Nonetheless, this website was ranked in the lowest two of the six websites most likely to be seen by searchers, with a WQA score of 11 (see Table 2). The FDA’s page Understanding Generic Drugs is a resource likely to be trusted by patients as it is written by the US pharmaceutical regulator. The lack of advertisements also lend the website a more professional, and possibly trustworthy, appearance than some of the other websites assessed during this study. The netdoctor.co.uk information on generic medicines, awarded the highest WQA score calculated during this study, was written by a pharmacist. This, like the MedicineNet site, may add weight to the content of this site in a searcher’s opinion. While there are a small number of adverts on this site, they are not as close to the information or as obvious as in other websites discussed above, and as such give the site a more
professional appearance. Finally, the WHO website, while being a reputable source which is likely to be recognised, trusted and possibly even sought out by searchers, unfortunately contains relatively little useful information for a searcher from the general public looking for information on generic medicines. Indeed, this was the lowest WQA scoring website of the six most likely to be viewed by searchers. Moreover, it additionally scored low for readability, indicating that this website is less likely to be used as a source of information by a searcher from the general public. Interestingly, 7 of the 15 websites that were discarded (i.e., not assessed by WQA) were sales websites. This strongly suggests that a searcher looking for information about generics may potentially be faced with a high number of websites selling generic medicines, representing a potential patient safety/public health risk given current concerns with counterfeit medicines being sold online [41]. Only one other website received the highest awarded WQA score (of 17) – a bulletin published by the National Medicines Information Centre at St. James’s hospital in Dublin, Ireland [42]. While the information in this article was of high quality the readability scores it received were relatively low. This is probably due to the fact that the intended audience of this bulletin was healthcare professionals and, thus, the language used in the article would have been appropriate. However, it would make it more difficult for a member of the general public to read, so while the information contained in this search result was very good, it may not be of use to a non-scientist. Therefore, for websites providing medical information to the general public, good information cannot stand alone; it must be used in conjunction with an assessment of the readability of the material. The language and syntax used must match the reading and comprehension abilities of the intended audience.

In the UK about 16% of adults are described as “functionally illiterate”, meaning that they have the literacy levels at or below those expected from an 11-year old [43].
Republic of Ireland the International Adult Literacy Survey revealed that one in four adults have problems with even the simplest of literacy tasks [44] with similar rates being seen in the US [45] and Canada [46]. A key finding of this study was that there is a correlation between good readability statistics and higher ranking on google.com searches (Table 4), indicating that more readable websites are more likely to be found by searchers. However, as the top scoring websites investigated during this study for Reading Ease scored relatively poorly for WQA, we were not able to investigate a website with both good information and good readability. Importantly, this could be construed to mean that when a searcher looks for information on generic medicines they are unlikely to find a website that is both readable and contains high quality information (as evidenced by a high WQA score). The implication is, therefore, that there is a gap in knowledge provision that could be filled by a website with high quality information, explaining to the general public specifically what generic medicines are (including dispelling any myths about generic drugs) which is also designed and written to maximize readability. Given the correlations between WQA score and readability statistics and ranking on google.com SERPs evinced by this study, it could reasonably be expected that such a website would return a highly placed score on a google.com SERP (across varying IP addresses). However, the finding of statistically significant correlations in this study was limited by the small sample sizes as the study was designed to mimic how a typical searcher would use a Google SERP (i.e., not going beyond the first page of results) [26]. An interesting question arising from this is: who is responsible for provision of such a website? Is it the responsibility of the State to provide good quality, readable medical information to its citizens? Or should it fall to private stakeholders to provide such a service? Recommendations from a 2010 report on the proposed model for introduction of generic substitution and reference pricing in Ireland stated that communication of information about generic medicines to the
general public would be key for the success of the proposed changes in the Irish healthcare system [47]. Whatever the answer, many patients using the Internet for medical information do not differentiate between high- and low-credibility sources of information when perceiving the quality of the information provided [48] and, therefore, it is clear that medical information websites need to be assessed for quality of information and readability by the intended audience before they are published on the Internet. The WQA tool developed during this evaluation of generic medicine-related site provides an easy-to-use tool for such an evaluation and may easily be adapted to assess other types of medical/healthcare information websites.
References


3. Mathieu E: The Internet and Medical Decision Making: Can It Replace the Role of Health Care Providers? Med Decis Making 2010, 30(5 suppl):14S-16S.


25. Operators and more search help


27. What is an IP address?

29. Using Microsoft Word’s Readability Program

[http://www.michbar.org/journal/pdf/pdf4article1467.pdf ; Archived at: http://www.webcitation.org/6FBcYBYCa]


42. **Generic Prescribing**


43. **How many illiterate adults are there in England?**

   [http://www.literacytrust.org.uk/adult_literacy/illiterate_adults_in_england]

   Archived at: [http://www.webcitation.org/6FBdF9w4m](http://www.webcitation.org/6FBdF9w4m)


45. **IALS Results** [http://nces.ed.gov/surveys/all/results.asp] Archived at: [http://www.webcitation.org/6FBdNgMBd](http://www.webcitation.org/6FBdNgMBd)

47. Proposed Model for Reference Pricing and Generic Substitution


Figure 1. Scatterplots of WQA score, Reading Ease score and Grade level against website ranking on US google.com search.
Figure 2. Scatterplots of readability assessments against WQA score (n=24 websites)

Note: the numbers refer to website titles in Table 3.
Table 1 – Website Quality Assessment (WQA) Questions for Assessing Generic Medicine Website Information

<table>
<thead>
<tr>
<th>Question</th>
<th>Answer and Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>23. Does the site give an explanation as to what a generic medicine is?</td>
<td>Yes = 1, No = 0</td>
</tr>
<tr>
<td>24. Is this explanation correct? (i.e. equivalent in dose, strength, route of administration, safety, efficacy, and intended use)</td>
<td>Yes = 1, No = 0</td>
</tr>
<tr>
<td>25. If so, is the explanation of a generic medicine readable and understandable by a non-scientist?</td>
<td>Yes = 1, No = 0</td>
</tr>
<tr>
<td>26. Are examples given of generic medicines? E.g., example of a proprietary medicine that also state their counterpart generic medicine?</td>
<td>Yes = 1, No = 0</td>
</tr>
<tr>
<td>27. Is bioequivalence mentioned in the website?</td>
<td>Yes = 1, No = 0</td>
</tr>
<tr>
<td>28. Is bioequivalence explained?</td>
<td>Yes = 1, No = 0, N/A</td>
</tr>
<tr>
<td>29. If so, is the explanation of bioequivalence correct?</td>
<td>Yes = 1, No = 0, N/A</td>
</tr>
<tr>
<td>30. If so, is the explanation of bioequivalence readable and understandable by a non-scientist?</td>
<td>Yes = 1, No = 0, N/A</td>
</tr>
<tr>
<td>31. Is the cheaper price of generics referred to?</td>
<td>Yes = 1, No = 0</td>
</tr>
<tr>
<td>32. Is an accurate reason for the cheaper price of generics given?</td>
<td>Yes = 1, No = 0, N/A</td>
</tr>
<tr>
<td>33. Is any inaccurate information regarding the cheaper price of generics given?</td>
<td>Yes = 0, No = 1, N/A</td>
</tr>
<tr>
<td>34. Are examples given of the actual price difference between generics and proprietary medicines, or of the amount of money that can be saved by use of generics?</td>
<td>Yes = 1, No = 0</td>
</tr>
<tr>
<td>35. Is reference made to the fact that approved, equivalent generic meds can have a different appearance (colour, shape etc.) different taste/smell or different inactive ingredients?</td>
<td>Yes = 1, No = 0</td>
</tr>
<tr>
<td>36. Are narrow therapeutic index [NTI] drugs mentioned?</td>
<td>Yes = 1, No = 0</td>
</tr>
<tr>
<td>Question</td>
<td>Answer and Score</td>
</tr>
<tr>
<td>-------------------------------------------------------------------------</td>
<td>------------------</td>
</tr>
<tr>
<td>37. Is the difference between NTI and non-NTI drugs explained?</td>
<td>Yes = 1</td>
</tr>
<tr>
<td></td>
<td>No = 0</td>
</tr>
<tr>
<td></td>
<td>N/A</td>
</tr>
<tr>
<td>38. Is there <em>accurate</em> information given on how generic bioequivalence, or generic manufacturing may affect NTI drugs?</td>
<td>Yes = 1</td>
</tr>
<tr>
<td></td>
<td>No = 0</td>
</tr>
<tr>
<td></td>
<td>N/A</td>
</tr>
<tr>
<td>39. Is any <em>inaccurate</em> information given regarding NTI drugs?</td>
<td>Yes = 0</td>
</tr>
<tr>
<td></td>
<td>No = 1</td>
</tr>
<tr>
<td></td>
<td>N/A</td>
</tr>
<tr>
<td>40. Are “pros” of generics mentioned? [e.g. lower price for same safety &amp; bioequivalence etc…]</td>
<td>Yes = 1</td>
</tr>
<tr>
<td></td>
<td>No = 0</td>
</tr>
<tr>
<td>41. Are any “cons” of generics mentioned? [e.g. adverse events to dissimilar excipients etc…]</td>
<td>Yes = 1</td>
</tr>
<tr>
<td></td>
<td>No = 0</td>
</tr>
<tr>
<td>42. Is the difference between proprietary and non-proprietary names mentioned?</td>
<td>Yes = 1</td>
</tr>
<tr>
<td></td>
<td>No = 0</td>
</tr>
<tr>
<td>43. Is the explanation given for the difference between proprietary and non-proprietary names accurate?</td>
<td>Yes = 1</td>
</tr>
<tr>
<td></td>
<td>No = 0</td>
</tr>
<tr>
<td></td>
<td>N/A</td>
</tr>
<tr>
<td>44. Generic prescribing mentioned and explained accurately?</td>
<td>Yes = 1</td>
</tr>
<tr>
<td></td>
<td>No = 0</td>
</tr>
<tr>
<td></td>
<td>TOTAL SCORE</td>
</tr>
<tr>
<td></td>
<td>Flesch Reading Ease Score</td>
</tr>
<tr>
<td></td>
<td>Flesch Kincaid Grade Level</td>
</tr>
<tr>
<td>Website title</td>
<td>Google SERP Ranking</td>
</tr>
<tr>
<td>------------------------------------------------------------</td>
<td>---------------------</td>
</tr>
<tr>
<td>1 Generic drug - Wikipedia, the free encyclopedia</td>
<td>1 1 1 1 1 1 1 1 1 1 16 49.1 10.2</td>
</tr>
<tr>
<td>2 Generic Drugs: Know the Benefits and Differences of Generic Drugs – about.com</td>
<td>2 2 2 3 2 2 10 6 16 53.5 8</td>
</tr>
<tr>
<td>3 Generic drugs, Are They as Good as Brand Names? - MedicineNet.com</td>
<td>3 3 3 5 5 3 3 2 11 42.5 11.3</td>
</tr>
<tr>
<td>4 Understanding Generic Drugs</td>
<td>4 5 4 6 3 4 6 7 16 57.2 9</td>
</tr>
<tr>
<td>5 Branded and generic medicines</td>
<td>5 7 6 2 6 9 17 36.7 14.6</td>
</tr>
<tr>
<td>6 WHO</td>
<td>Generic Drugs</td>
</tr>
<tr>
<td>7 RxList – Facts About Generic Drugs</td>
<td>7 6 4 8 9 79.3 4.6</td>
</tr>
<tr>
<td>8 EGA - European Generic medicines Association</td>
<td>8 9 8 13 22.9 12</td>
</tr>
<tr>
<td>9 National Medicines Information</td>
<td>8 17 31 11.5</td>
</tr>
</tbody>
</table>

Table 2: Websites assessed with their rankings on the different Google searches and Website Quality Assessment (WQA) score
<table>
<thead>
<tr>
<th>Centre - Generic Prescribing</th>
<th>10</th>
<th>15</th>
<th>25</th>
<th>17.1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Generic Drugs - What are Generic Drugs?</td>
<td>10</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GPhA - Generic Pharmaceutical Association</td>
<td>9</td>
<td>7</td>
<td>9</td>
<td>14</td>
</tr>
<tr>
<td>Generic / Brand Drug Name Table</td>
<td>10</td>
<td>10</td>
<td>3</td>
<td>10</td>
</tr>
<tr>
<td>Generic vs. Brand Name Medicines</td>
<td>4</td>
<td>9</td>
<td>60</td>
<td>8</td>
</tr>
<tr>
<td>AIDS, Drug Prices and Generic Drugs</td>
<td>9</td>
<td>10</td>
<td></td>
<td>11</td>
</tr>
<tr>
<td>Canadian Generic Pharmaceutical Association</td>
<td>2</td>
<td></td>
<td></td>
<td>12</td>
</tr>
<tr>
<td>Generics Are The Same</td>
<td>(2)b</td>
<td>12</td>
<td>43.7</td>
<td>12.5</td>
</tr>
<tr>
<td>Generic Drugs In Canada: A Policy Paper</td>
<td>4</td>
<td>8</td>
<td>37.3</td>
<td>14</td>
</tr>
<tr>
<td>Benefiting from Generic Drug Competition in Canada: The Way Forward</td>
<td>7</td>
<td>11</td>
<td>54.4</td>
<td>7.7</td>
</tr>
<tr>
<td>Generic Drugs – The Same Medicine for Less Money</td>
<td>7</td>
<td>10</td>
<td>75.1</td>
<td>5.6</td>
</tr>
<tr>
<td>Generic Drugs</td>
<td>9</td>
<td>6</td>
<td>42</td>
<td>11.9</td>
</tr>
<tr>
<td>The Generic Medicines industry Association of Australia</td>
<td>3</td>
<td>13</td>
<td>24.4</td>
<td>12</td>
</tr>
<tr>
<td>Australian Prescriber: Frequently</td>
<td>4</td>
<td>15</td>
<td>22.2</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>asked questions about generic medicines</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>---</td>
<td>----------------------------------------</td>
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<td>---</td>
</tr>
<tr>
<td>23</td>
<td>Pricing of PBS Medicine - Medicare Australia</td>
<td></td>
<td></td>
<td>8</td>
</tr>
<tr>
<td>10</td>
<td>34.3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24</td>
<td>Questions and answers on generic medicines</td>
<td></td>
<td></td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>32.9</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*a Abbreviations used: IE = Ireland, UK = United Kingdom, US = United States, CA = Canada, AU = Australia

*b This website “Generics Are The Same” was not a result in the original searches, but was directly linked to the Canadian Generic Pharmaceutical Association website, which was the second result returned in the google.ca search. As it is likely that a patient finding the first website would link into the second, it was added to this study and WQA assessed with the other websites found.
<table>
<thead>
<tr>
<th>Website number</th>
<th>Website title</th>
<th>URL</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Generic drug - Wikipedia, the free encyclopedia</td>
<td>en.wikipedia.org/wiki/Generic_drug</td>
</tr>
<tr>
<td>2</td>
<td>Generic Drugs: Know the Benefits and Differences of Generic Drugs</td>
<td>patients.about.com/od/drugsandsafety/a/genericdrugs.htm</td>
</tr>
<tr>
<td>3</td>
<td>Generic drugs, Are They as Good as Brand Names?</td>
<td><a href="http://www.medicinenet.com/script/main/art.asp?articlekey=46204">http://www.medicinenet.com/script/main/art.asp?articlekey=46204</a></td>
</tr>
<tr>
<td>4</td>
<td>Understanding Generic Drugs</td>
<td><a href="http://www.fda.gov/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/UnderstandingGenericDrugs/default.htm">http://www.fda.gov/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/UnderstandingGenericDrugs/default.htm</a></td>
</tr>
<tr>
<td>5</td>
<td>Branded and generic medicines</td>
<td><a href="http://www.netdoctor.co.uk/medicines/brandGeneric.htm">www.netdoctor.co.uk/medicines/brandGeneric.htm</a></td>
</tr>
<tr>
<td>8</td>
<td>EGA - European Generic medicines Association</td>
<td><a href="http://www.egagenerics.com">www.egagenerics.com</a></td>
</tr>
<tr>
<td>10</td>
<td>Generic Drugs - What are Generic Drugs?</td>
<td><a href="http://www.news-medical.net/health/Generic-Drugs-What-are-Generic-Drugs.aspx&amp;sa=U&amp;ei=EZlPT6aeGsm0hAek5_37Cw&amp;ved=0CEoQFjAL&amp;usg=AFQjCNGQGB3LydlBdSlK0yRYr7zC0ubexQ">www.news-medical.net/health/Generic-Drugs-What-are-Generic-Drugs.aspx&amp;sa=U&amp;ei=EZlPT6aeGsm0hAek5_37Cw&amp;ved=0CEoQFjAL&amp;usg=AFQjCNGQGB3LydlBdSlK0yRYr7zC0ubexQ</a></td>
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<tr>
<td>11</td>
<td>GPhA - Generic Pharmaceutical Association</td>
<td><a href="http://www.gphaonline.org/">www.gphaonline.org/</a></td>
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<tr>
<td>12</td>
<td>Generic / Brand Drug Name Table</td>
<td><a href="http://www.health.gov.bc.ca/pharmacare/sa/criteria/genericbrandtable.h">http://www.health.gov.bc.ca/pharmacare/sa/criteria/genericbrandtable.h</a></td>
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<td>13</td>
<td>Generic vs. Brand Name Medicines</td>
<td><a href="http://www.patient.co.uk/health/Generic-vs-Brand-Name-Medicines.htm">www.patient.co.uk/health/Generic-vs-Brand-Name-Medicines.htm</a></td>
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<td>14</td>
<td>AIDS, Drug Prices and Generic Drugs</td>
<td><a href="http://www.avert.org/generic.htm">www.avert.org/generic.htm</a></td>
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<td>Canadian Generic Pharmaceutical Association</td>
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<td>16</td>
<td>Generics Are The Same</td>
<td><a href="http://www.genericsarethensame.com/">www.genericsarethensame.com/</a></td>
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<td>22</td>
<td>Australian Prescriber: Frequently asked questions about generic medicines</td>
<td><a href="http://www.australianprescriber.com/magazine/30/2/41/3">www.australianprescriber.com/magazine/30/2/41/3</a></td>
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Table 4: Correlation Between WQA, Reading Ease Score And Grade Level With Ranking Using Spearman’s Correlation Coefficient ($r_s$)

<table>
<thead>
<tr>
<th>Google Domain</th>
<th>n</th>
<th>WQA Spearman’s $r_s$</th>
<th>p-value</th>
<th>Flesch Reading Ease Score Spearman’s $r_s$</th>
<th>p-value</th>
<th>Flesch Kincaid Grade level Spearman’s $r_s$</th>
<th>p-value</th>
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<td>IE / .com</td>
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<td>0.220</td>
<td>-0.33</td>
<td>0.420</td>
<td>0.24</td>
<td>0.570</td>
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<td>IE / .ie</td>
<td>10</td>
<td>0.06</td>
<td>0.866</td>
<td>-0.64*</td>
<td>0.048*</td>
<td>0.58</td>
<td>0.082</td>
</tr>
<tr>
<td>UK / .com</td>
<td>8</td>
<td>-0.38</td>
<td>0.352</td>
<td>-0.48</td>
<td>0.233</td>
<td>0.43</td>
<td>0.289</td>
</tr>
<tr>
<td>UK / .co.uk</td>
<td>9</td>
<td>-0.51</td>
<td>0.160</td>
<td>-0.58</td>
<td>0.112</td>
<td>0.44</td>
<td>0.232</td>
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<td>US / .com</td>
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<td>0.68</td>
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</tr>
<tr>
<td>CA / .com</td>
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<td>0.10</td>
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<td>0.493</td>
<td>-0.38</td>
<td>0.352</td>
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<tr>
<td>AU / .com.au</td>
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<td>-0.10</td>
<td>0.787</td>
<td>0.00</td>
<td>1.000</td>
<td>0.33</td>
<td>0.359</td>
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</table>

*Statistically significant at 5% level of significance.
## List of abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>AU</td>
<td>Australia</td>
</tr>
<tr>
<td>CA</td>
<td>Canada</td>
</tr>
<tr>
<td>EGA</td>
<td>European Generic Medicines Association</td>
</tr>
<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
</tr>
<tr>
<td>ICC</td>
<td>Intraclass Correlation Coefficient</td>
</tr>
<tr>
<td>IE</td>
<td>Ireland</td>
</tr>
<tr>
<td>IP</td>
<td>Internet Protocol</td>
</tr>
<tr>
<td>SERP</td>
<td>Search Engine Results Page</td>
</tr>
<tr>
<td>UK</td>
<td>United Kingdom</td>
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<tr>
<td>US</td>
<td>United States</td>
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<tr>
<td>WHO</td>
<td>World Health Organisation</td>
</tr>
<tr>
<td>WQA</td>
<td>Website Quality Assessment</td>
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</table>
Declaration of competing interests

All authors declare that they have no competing interests.

Contributorship statement

SD conceived of the idea for the research, designed and conducted the analysis, gathered and interpreted the data and drafted, revised and finalised the manuscript.

NC aided in data gathering and interpretation and provided critical review of the manuscript.

AH completed statistical analysis of the data, provided critical review of the manuscript and final approval of the version to be published.

BS provided critical review of the manuscript and final approval of the version to be published.

CD provided critical review of the manuscript and final approval of the version to be published.

WC provided critical review of the manuscript and final approval of the version to be published.

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Chapter 10

What answers does the Internet provide for Irish patients with questions about generic medicines?


Citation:
What answers does the Internet provide for Irish patients with questions about generic medicines?

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Abstract

Background
Use of generic medicines in Ireland has historically been low. New legislation, planned for implementation in 2013, will introduce reference pricing and generic substitution in Ireland for the first time. Also, as patents have recently expired for many familiar medicines, Irish patients are more likely than ever to receive a generic medicine.

Aims
As the Internet is a primary source of information for patients seeking information on healthcare matters, this study aims to assess - in terms of quality and accessibility - information on generic medicines that an Irish searcher is likely to find online.

Methods
Internet searches were completed using a computer with an Irish Internet Protocol (IP) address. Search results were evaluated with respect to quality of information, using a newly developed Website Quality Assessment (WQA) tool, and for readability, using existing methods. The reproducibility of the tools was assessed and correlations between WQA score, readability statistics and Google search engine results page (SERP) ranking were determined.

Results
This novel and topical evaluation showed that, of the websites most likely to be seen by a searcher, none demonstrated the desired combination of scoring highly for both quality of information and readability.

Conclusions
Patient education is a key factor in implementation of the changes planned in the Irish healthcare system. There is a gap in online knowledge provision in Ireland which, if filled by a website designed using the WQA tool developed in this study, will correct this deficit by providing accessible, high-quality information.
Keywords

Google SERP ranking, generic medicine, Internet, medical information, patient education, readability
Introduction

Irish healthcare spending in 2010 accounted for 9.2% of GDP [1], with total expenditure on pharmaceuticals amounting to €2.2 billion, and public expenditure on pharmaceuticals (administered by the Primary Care Reimbursement Service, PCRS) amounting to €1.9 billion. Public expenditure on pharmaceuticals was amongst the fastest growing components of public health expenditure over the period 2000 to 2010. It increased by 158.5% in real terms and accounted for 12.9% of total public health expenditure in 2010 (up from 10.1% in 2000) [1].

Historically, Ireland’s usage of generic medicines has been low relative to many other European countries. Information from the European Generic Medicines Association (EGA) stated that the volume of generic medicines used in Ireland in 2006 was approximately 5% and in a report written by the National Centre for Pharmacoeconomics (NCPE) for the Irish Department of Health and Children (DOHC) in 2008 it was reported that generic prescribing in Ireland had fallen from over 22% by volume in 1997 to just over 19% in 2007 [2]. As a result of this poor penetration by generic medicines, Irish expenditure per 1000 inhabitants per annum is ten times that of Sweden, putting in perspective the considerable need to quickly realize the substantial savings that are possible without compromising patient safety or efficacy of treatment.

In the context of the current global economic downturn and the impact it is having on the Irish economy, the Irish government has explored many options to curtail public spending. In the healthcare system, a decision was made to benefit from cost-savings associated with use of generic medicines through introduction of generic substitution and reference pricing. When this change comes into force with the new legislation (The Health (Pricing and Supply of Medical Goods) Bill 2012) that is planned for 2013 [3], it is likely that patients will receive greater amounts of generic medicines in the future.
When a patient is faced with using a generic medicine, possibly in place of a trusted brand-name medicine, the Internet is likely to be one of the first resources that they will turn to in order find information about what generic medicines are and how they may differ from proprietary medicines.

Hence, this study asks the question: what is the quality and accessibility of information, regarding generic medicines, that Irish patients are likely to find on the Internet?
Methods

Choice of Search Engine

StatCounter, a web analytics company, reports in their “GlobalStats graph” that - for the 12 month period from Jan 2012 to Jan 2013 - Google was the most commonly used search engine globally, holding approximately 90% of the worldwide search engine market [4]. Therefore, as Google is the search engine of choice globally, Google was the search engine used for this study (www.google.ie and www.google.com).

Choice of Search Term

A patient wishing to make an Internet enquiry about a generic medicine is likely to use either the term “generic drug” or “generic medicine” as their search term. To accommodate both of these terms, the search term used for this study was “generic medicine OR drug” (without the quotation marks, and with the “OR” capitalised). Our rationale is that Google's default behaviour is to consider all the words in a search. In order to allow either of the words “drug” or “medicine” to be searched for, the “OR” operator can be used (the OR must be in capitals). With this search, Google will return SERP hits that contain the word “generic” and either of the words “drug” or “medicine”. Without the “OR” operator, Google would only return Search Engine Results Pages (SERPs) that have both the words “drug” and “medicine” on the page, as the “AND” operator is the default [5].

Searches were done during March 2012.

Inclusion of Web Sites

A study from 2008 showed that 68% of search engine users click a search result within the first page of results (the default for Google is 10 results per page) [6] and are unlikely to go to the second page of search results. Therefore, following a search using
the identified search term, the results on the first SERP returned, that meet the following inclusion criteria, were assessed: (i) website is written in English; (ii) website is not a portal serving to provide links to third party sites; (iii) website is not a news story (e.g., as found by the Google news search); (iv) website is not a sales website and (v) website is not spurious and is related to the topic of generic medicines.

Determination of Variability Associated with Domain

In order to fully determine any search results that could be seen by an Irish searcher, searches were performed using both google.ie and google.com on a computer with an Irish IP address. (IP stands for “Internet Protocol”. Every device (e.g., computer, tablet, printer etc.) on a computer network has a unique, numeric identifier called an IP address. Analogous to how someone sending a letter would write the intended address on the envelope, a computer’s IP address is used to identify and locate that specific device on a computer network, or on the Internet [7]).

Assessment of Quality of Information

The questions in Table 1 – Website Quality Assessment (WQA) Questions for Website Information – were asked in relation to each website. The WQA tool consists of 22 yes/no type questions, where a point is awarded for positive or correct information. No points are awarded where information was lacking, or for inaccurate information. Questions that could not be answered were designated “not applicable” (N/A) and no score awarded. An overall WQA score for each website was aggregated from the scores given to each assessment question.

The questions in the WQA were designed to account for all of the information that a patient might need in order to accurately answer any questions they may have about generic drugs, for example: an explanation as to what a generic drug is and how it
differs from a proprietary drug – including price, appearance etc.; explanation of bioequivalence; examples of generic drugs and their proprietary counterparts; information regarding when generic substitution may not be appropriate, such as in the case of narrow therapeutic index drugs, and any pros or cons of generic medicines.

Two reviewers independently rated each selected website and their scores were compared to assess reproducibility of its usage in order to validate the assessment tool.

**Assessment of Website Readability**

A minimum of a 100-word sample of continuous text from each of the websites was extracted and imported into MS Word. This text was then analysed using the Flesch Reading Ease score [8] in the Word application.

Word’s Flesch Reading Ease score is based on a formula developed in 1948 by Rudolf Flesch [8]. It is computed using the average number of syllables per word and words per sentence. Syllables-per-word is a measure of word difficulty. Words-per-sentence is an indicator of syntactic complexity.

The Flesch Reading Ease scale ranges from zero to 100. Zero to 50 is very difficult to difficult reading. Eighty and above is easy to very easy reading. Flesch himself set the minimum score for plain English at 60 [8]. Microsoft’s documentation encourages authors of standard documents to aim for a score of 60 to 70 [9, 10].

Additionally, the Flesch-Kincaid Grade Level was used to determine the readability score for each website. The Flesch-Kincaid Grade Level, which was developed in 1975, measures the readability of a document based on the minimum education level required for a reader to understand it [11]. Microsoft recommends aiming for a Flesch-Kincaid score of 7.0 to 8.0 for most documents. According to a 1993 study, the average adult in the U.S. reads at the seventh-grade level and the authors of that study recommended that materials for the public be written at a fifth- or sixth-grade reading level [9]. Fifth
and sixth grades in the US equate to the last two years of primary school in Ireland (fifth and sixth class) and seventh and eighth grades in the US are the equivalent of the first two years of secondary school in Ireland (first and second year).

**Statistical Analyses**

Two reviewers independently rated each selected website and their scores were compared to assess reproducibility of the WQA tool and the readability assessments. The intraclass correlation coefficient (ICC) was used to measure reproducibility between reviewers’ independent ratings. Scatter plots and Spearman's correlation coefficient were used to describe and measure the association between the ranking of websites with WQA scores and readability assessments. The scores from the developer of the assessment tool (SD) were used in the correlation analyses.
Results

Determination of Websites for Assessment

Twelve (12) unique hits were identified from the first SERPs of the two searches performed. Of these, 2 hits were discarded, as they were sales websites. Therefore, a total of 10 individual websites were assessed using the Website Quality Assessment tool. Results of the assessments for each of the websites are displayed in Table 2, which additionally shows the ranking on the Google SERP for each website assessed, in the two different domains (i.e., google.ie and google.com).

Analysis of Websites from Search Results

Visual analysis of the search results (Table 2) showed that Wikipedia (a collaboratively edited, multilingual, free Internet encyclopedia supported by the non-profit Wikimedia Foundation) was the number one ranked search result in both of the searches completed. This is consistent with findings in other studies [12, 13]. Wikipedia is the 6th most accessed website on the Internet globally [14] and both this fact and the results from this study demonstrate that Wikipedia is highly likely to be visited by Irish information seekers, including those seeking medical/healthcare information.

The majority of the search results obtained were common to both Irish SERPs with the exception of two websites, (i) the National Medicines Information Centre bulletin on Generic Prescribing and (ii) news-medical.net’s page entitled What Are Generic Drugs? which appeared only in the google.ie search. The corresponding two websites seen in the google.com search were sales websites, which were discarded and, therefore, not assessed.
**WQA Scores**

The WQA tool (Table 1) employed the use of 22 yes/no type questions to assess the quality of information contained in each website. None of the websites assessed scored the maximum achievable score of 22. The highest score awarded during the WQA rating exercise was 17 - awarded to two websites: (i) Netdoctor.co.uk’s page entitled *Branded and Generic Medicines* and (ii) a bulletin on Generic Prescribing from the National Medicines Information Centre in St. James’s hospital, Dublin.

Six of the websites assessed achieved a WQA score of 15 or greater, as can be seen from the information in Table 2. The lowest score awarded was a WQA of 9.

Figure 1 (a) describes the relationship between WQA scores and ranking of the websites in the google.com search indicating that websites ranked higher (1, 2, etc.) tended to have higher WQA scores. The relationship between WQA scores and ranking was strong in the google.com search (Spearman’s correlation coefficient $r_s=-0.49$) although no relationship was found between rankings and WQA score in the google.ie search (Figure 1 (b)).

**Readability scores**

A Flesch Reading Ease score of 60 or greater and a Flesch Kincaid Grade Level of less than 8 are recommended for general ease of reading. Only one of the websites assessed had a Reading Ease score of greater than or equal to 60 – the rxlist.com page *Facts About Generic Drugs*. This website also scored well for Flesch Kincaid Grade Level, with a score of 4.6; however, it scored relatively poorly for quality of information as determined by WQA, with a score of 9 out of a possible maximum of 22 – the lowest WQA score awarded during this study. All of the other websites assessed had Reading Ease scores below 60, indicating that they might not be very accessible to the general public.
Only one additional website had a Flesch Kincaid Grade Level score of 8 or less: the patients.about.com page *Generic Drugs: Know the Benefits and Differences of Generic Drugs*. This website scored reasonably well on WQA, achieving a score of 16.

In fact, the highest scoring websites for WQA had relatively poor Reading Ease and Grade Level scores – indicating, again, a potential lack of accessibility of the material contained therein to members of the general public.

Figure 1 (c) and (d) describe the relationship between Reading Ease scores and ranking of the websites in the google.com and google.ie searches. In general, the top ranked sites (placed 1, 2, etc.) tended to have the higher reading ease scores in the google.ie search ($r_s = -0.64$). A moderate relationship was found in the google.com search ($r_s = -0.33$). A strong relationship between Flesch-Kincaid Grade Level and ranking of websites was found for the google.ie search ($r_s = 0.58$) indicating that the top ranked sites tended to have lower values for grade level. The relationship between grade level and website ranking was weaker, however, in the google.com search ($r_s = 0.24$). Figure 1 (e) and (f) describe the relationship between Flesch-Kincaid Grade Level scores and ranking of the websites in the google.com and google.ie searches.

**Reproducibility**

Comparison of the scores of the two independent reviewers (SD and NC) shows that, for WQA assessments of the websites, almost perfect agreement was seen (ICC = 0.97).

Similar analysis of the readability of the websites using Flesch Reading Ease score and Flesch-Kincaid Grade Level showed moderate to strong levels of agreement between the two reviewers. (ICC value = 0.69 and 0.52 respectively).

Readability scores were assessed by taking a section of text from the website and calculating readability statistics using MS Word. As each rating was independent, different sections of text were likely to be taken from each of the websites assessed.
This variation in the text taken is likely to account for the lower levels of agreement for the reading assessments, compared to the WQA tool. Given the subjectivity of this type of readability assessment, and the possible variability in the text selected by reviewers for assessment, it is reasonable to state that a moderate consistency in the writing throughout the websites assessed was observed.

Overall the WQA and readability scores demonstrate acceptable reproducibility between two independent reviewers.
Discussion

With the imminent coming into force of new legislation introducing generic substitution and reference pricing into the Irish healthcare system for the first time [3], Irish patients are far more likely to receive generic medicines than any time in the past – particularly when Ireland’s relatively poor record of generic medicines usage is taken into account [15]. Usage of generics in Ireland was at 19% in 2007 [2] compared, for example, to approximately 83% in the UK [16], thus providing considerable scope for cost savings in the Irish drug budget with little impact on patient welfare. An increase in use of generics is associated with significant cost savings, for example in 2010 alone, the use of generics in the American health system saved $158 billion, an average of $3 billion every week [17] and a study by the Generic Pharmaceutical Association (GPhA) showed that prescribing of generics has saved the US economy $931 billion between 2001 and 2010 [18]. Analogous savings may be possible in Ireland.

As many misconceptions exist about generic medicines, and given that some healthcare professionals have expressed poor opinions of generics in the past [15], there is a challenge in ensuring that accurate and relevant information is communicated to the general public. This challenge includes not only the necessity to provide accurate information (including facts on both positive and perceived-negative factors), to dispel myths and to counter misinformation, but also to present the material in a manner that is accessible to the intended audience. It has been reported that, in the case of patients particularly, misconceptions and questions abound or persist about generic medicines, and that accurate information can be difficult to come by [19].

In the context that the Internet is one of the first places a patient is likely to go when they are looking for medical/healthcare information [20], this study has shown that an Irish patient searching the Internet for information about generic medicines is unlikely to find a website that has both high quality information (as determined by WQA
ranking) and is widely accessible to a lay-audience (as measured by readability statistics). While websites that contain high quality information (achieving 16-17 in WQA scores) are likely to be found by Irish searchers, none of the websites that an Irish patient is most probably going to be led to by a Google search contain all of the material that the authors believe would provide accurate and unbiased information (as would have been seen by a WQA score closer to the maximum of 22). Moreover, none of the websites assessed in this study were awarded both a high WQA score in combination with good readability indicators. The conclusion is, therefore, that there is a gap which could be filled by a good quality website, designed using the WQA tool described in this study, containing all of the information necessary for a patient to educate themselves and make informed decisions about any generic medication they may be taking – and which is also easily read and understood by most members of the general public. By ensuring that such a website was developed in this manner, not only would the website be accessible to more patients, but it would also be more likely to rank higher on a google.com SERP.

One of the two websites that received the highest awarded WQA score (of 17) was a bulletin published by the National Medicines Information Centre at St. James’s hospital in Dublin [21]. While the information in this article was of high quality, the readability scores it received were relatively low. This is undoubtedly due to the fact that the intended audience of this bulletin was healthcare professionals and, thus, the language used in the article was appropriate. However, it would make it more difficult for a member of the general public to read, so while the information contained in this search result was very good, it may not be of use to, or even read by, a patient.

Therefore, for websites providing medical information to the general public, good information cannot stand alone; it must be used in conjunction with an assessment of the readability of the material. The language and syntax used must match the reading
and comprehension abilities of the intended audience. The International Adult Literacy Survey revealed that one in four adults in Ireland have problems with even the simplest of literacy tasks [22], therefore, a key factor in the provision of published medical/healthcare information to patients is the readability of the text provided. This point applies, of course, not only to online information, but also to any printed material provided to patients.

The question remains as to who should be responsible for provision of such a website? As recommendations from a 2010 report on the proposed model for introduction of generic substitution and reference pricing in Ireland stated that communication of information about generic medicines to the general public would be a key factor for the success of the proposed change in the Irish healthcare system [23], it could be argued that the government, or the Irish Health Services Executive, has a role to play in providing this information to Irish patients. Whatever the answer, many patients using the Internet for medical information do not differentiate between high- and low-credibility sources of information [24] and, so, it is clear that any medical information websites provided to Irish patients need to be assessed for quality of information and readability by the intended audience before they are published on the Internet. As such, the WQA tool, used here for evaluation of websites providing information on generic medicines, may be readily adapted to assess a wide range of other medical/healthcare information websites.
Acknowledgements

This work was supported in part by a scholarship from the Faculty of Education and Health Sciences, University of Limerick, Ireland.

Conflicts of Interest

The authors have no conflicts of interest.
References


5. **Operators and more search help** [http://www.google.com/support/websearch/bin/answer.py?answer=136861-exceptions Archived at: http://www.webcitation.org/6HRbOiNNf]


7. **What is an IP address?** [http://www.howstuffworks.com/internet/basics/question549.htm Archived at: http://www.webcitation.org/6HRVBXxMe]


21. Generic Prescribing


23. Proposed Model for Reference Pricing and Generic Substitution

<table>
<thead>
<tr>
<th>Question</th>
<th>Answer and Score</th>
<th>WQA Score awarded</th>
</tr>
</thead>
<tbody>
<tr>
<td>Does the site give an explanation as to what a generic medicine is?</td>
<td>Yes = 1  No = 0</td>
<td></td>
</tr>
<tr>
<td>Is this explanation correct? (i.e. equivalent in dose, strength, route of administration, safety, efficacy, and intended use)</td>
<td>Yes = 1  No = 0</td>
<td></td>
</tr>
<tr>
<td>If so, is the explanation of a generic medicine readable and understandabe by a non-scientist?</td>
<td>Yes = 1  No = 0</td>
<td></td>
</tr>
<tr>
<td>Are examples given of generic medicines? E.g. example of a proprietary medicine that also state their counterpart generic medicine?</td>
<td>Yes = 1  No = 0</td>
<td></td>
</tr>
<tr>
<td>Is bioequivalence mentioned in the website?</td>
<td>Yes = 1  No = 0</td>
<td></td>
</tr>
<tr>
<td>Is bioequivalence explained?</td>
<td>Yes = 1  No = 0  N/A</td>
<td></td>
</tr>
<tr>
<td>If so, is the explanation of bioequivalence correct?</td>
<td>Yes = 1  No = 0  N/A</td>
<td></td>
</tr>
<tr>
<td>If so, is the explanation of bioequivalence readable and understandable by a non-scientist?</td>
<td>Yes = 1  No = 0  N/A</td>
<td></td>
</tr>
<tr>
<td>Is the cheaper price of generics referred to?</td>
<td>Yes = 1  No = 0</td>
<td></td>
</tr>
<tr>
<td>Is an <em>accurate</em> reason for the cheaper price of generics given?</td>
<td>Yes = 1  No = 0  N/A</td>
<td></td>
</tr>
<tr>
<td>Is any <em>inaccurate</em> information regarding the cheaper price of generics given?</td>
<td>Yes = 0  No = 1  N/A</td>
<td></td>
</tr>
<tr>
<td>Are examples given of the actual price difference between generics and proprietary medicines, or of the amount of money that can be saved by use of generics?</td>
<td>Yes = 1  No = 0</td>
<td></td>
</tr>
<tr>
<td>Is reference made to the fact that approved, equivalent generic meds can have a different appearance (colour, shape etc.) different taste/smell or different inactive ingredients?</td>
<td>Yes = 1  No = 0</td>
<td></td>
</tr>
<tr>
<td>Are narrow therapeutic index [NTI] drugs mentioned?</td>
<td>Yes = 1  No = 0</td>
<td></td>
</tr>
<tr>
<td>Is the difference between NTI and non-NTI drugs explained?</td>
<td>Yes = 1  No = 0  N/A</td>
<td></td>
</tr>
<tr>
<td>Is there <em>accurate</em> information given on how generic bioequivalence, or generic manufacturing may affect NTI drugs?</td>
<td>Yes = 1  No = 0  N/A</td>
<td></td>
</tr>
<tr>
<td>Is any <em>inaccurate</em> information given regarding NTI drugs?</td>
<td>Yes = 0  No = 1</td>
<td></td>
</tr>
<tr>
<td>Question</td>
<td>Answer and Score</td>
<td>WQA Score awarded</td>
</tr>
<tr>
<td>-------------------------------------------------------------------------</td>
<td>------------------</td>
<td>-------------------</td>
</tr>
<tr>
<td>Are “pros” of generics mentioned? [e.g. lower price for same safety &amp; bioequivalence etc…]</td>
<td>Yes = 1</td>
<td>N/A</td>
</tr>
<tr>
<td>Are any “cons” of generics mentioned? [e.g. adverse events to dissimilar excipients etc…]</td>
<td>Yes = 1</td>
<td>No = 0</td>
</tr>
<tr>
<td>Is the difference between proprietary and non-proprietary names mentioned?</td>
<td>Yes = 1</td>
<td>No = 0</td>
</tr>
<tr>
<td>Is the explanation given for the difference between proprietary and non-proprietary names accurate?</td>
<td>Yes = 1</td>
<td>No = 0</td>
</tr>
<tr>
<td>Generic prescribing mentioned and explained accurately?</td>
<td>Yes = 1</td>
<td>No = 0</td>
</tr>
</tbody>
</table>

**TOTAL SCORE**

Flesch Reading Ease Score

Flesch Kincaid Grade Level
Table 2: Search Results and Associated SERP Ranks with WQA and Readability Scores.

<table>
<thead>
<tr>
<th>No.</th>
<th>Website title</th>
<th>google.com</th>
<th>googl e.ie</th>
<th>WQA Score</th>
<th>Flesch Reading Ease Score</th>
<th>Flesch Kincaid Grade Level</th>
<th>URL</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Generic drug - Wikipedia, the free encyclopedia</td>
<td>1</td>
<td>1</td>
<td>16</td>
<td>49.1</td>
<td>10.2</td>
<td>en.wikipedia.org/wiki/Generic_drug</td>
</tr>
<tr>
<td>2</td>
<td>Generic Drugs: Know the Benefits and Differences of Generic Drugs – about.com</td>
<td>2</td>
<td>2</td>
<td>16</td>
<td>53.5</td>
<td>8</td>
<td>patients.about.com/od/drugsandsafety/a/genericdrugs.htm</td>
</tr>
<tr>
<td>3</td>
<td>Generic drugs, Are They as Good as Brand Names? - MedicineNet.com</td>
<td>3</td>
<td>3</td>
<td>11</td>
<td>42.5</td>
<td>11.3</td>
<td><a href="http://www.medicinenet.com/script/main/art.asp?articlekey=46204">http://www.medicinenet.com/script/main/art.asp?articlekey=46204</a></td>
</tr>
<tr>
<td>4</td>
<td>Understanding Generic Drugs</td>
<td>4</td>
<td>5</td>
<td>16</td>
<td>57.2</td>
<td>9</td>
<td><a href="http://www.fda.gov/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/UnderstandingGenericDrugs/default.htm">http://www.fda.gov/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/UnderstandingGenericDrugs/default.htm</a></td>
</tr>
<tr>
<td>5</td>
<td>Branded and generic medicines</td>
<td>5</td>
<td>7</td>
<td>17</td>
<td>36.7</td>
<td>14.6</td>
<td><a href="http://www.netdoctor.co.uk/medicines/brand_generic.htm">www.netdoctor.co.uk/medicines/brand_generic.htm</a></td>
</tr>
<tr>
<td>6</td>
<td>WHO</td>
<td>Generic Drugs</td>
<td>6</td>
<td>4</td>
<td>10</td>
<td>32.9</td>
<td>13.7</td>
</tr>
<tr>
<td>8</td>
<td>EGA - European Generic medicines Association</td>
<td>8</td>
<td>9</td>
<td>13</td>
<td>22.9</td>
<td>12</td>
<td><a href="http://www.egagenerics.com">www.egagenerics.com</a></td>
</tr>
</tbody>
</table>
Figure 1. Scatterplots of WQA score, Reading Ease score and Grade level against website ranking on IE google.com and google.ie searches.
Summary Conclusion
Summary Conclusion

Generic medicines are a necessary part of cost-control in modern healthcare systems and, internationally, their usage has been steadily increasing over the past decade. In many countries generic medicines account for approximately 80% of the volume of medicines consumed and, while in some cases clinical issues have been associated with usage of these medicines (issues and concerns with narrow therapeutic index drugs notwithstanding), in the vast majority of cases there is no negative clinical impact associated with using these cost effective drugs.

This thesis has elucidated, for the first time in Ireland, the opinions and perceptions held by pharmacists and patients towards generic medicines, and have provided new, up-to-date information on the opinions, perceptions and behaviours of GPs (the first Irish study since 1997). These studies have shown that while healthcare professionals tend to have generally positive views towards generics and demonstrate a high degree of confidence in their use, the same is not true of the patient population. This thesis provides evidence that, since 1997, GP perceptions of generic medicines have improved - GPs in 2012 were more favourably disposed towards prescription of generics than was demonstrated in the 1997 study - thus showing that in the intervening period, a general shift in opinion in favour of generics has occurred in the Irish GP cohort. However, these studies have shown that some GP reticence remains towards generic medicines, which may have an impact on the already poor opinion that appears to be held by a large proportion of the patient/consumer group. The overwhelming theme emerging from these investigations is that information and education provision is essential – for all groups, professional as well as general public.

The innovative WQA tool that was developed as part of this thesis may be used in the design, development or assessment of healthcare information websites. Specifically, this tool ensures not only that websites contain the correct, accurate information, but also
that they are written in such a way that the information is accessible by and appropriate to the intended audience. Moreover, existing websites can be assessed using this tool, as was done for websites providing information on generic medicines in a variety of native English speaking countries, and where issues are noted, remediation measures implemented.

Future work deriving from this thesis may focus firstly on the utilisation of the data collected during the interview studies. These studies provide a unique resource elucidating Irish stakeholder opinions in the time period immediately preceding the implementation of the Health (Pricing and Supply of Medical Goods) Act, 2013. As such, these data may represent a baseline for comparative studies assessing the acceptance, or otherwise, of the changes implemented and the changing perceptions of stakeholders towards generic medicines in the future. Secondly, in the context of current interest in generic medicine-related and more general healthcare information provision, there is a clear opportunity to build on the time and resources which were invested in developing the innovative WQA tool by partnering with those designing healthcare/medical information websites.

In summary, these investigations impart new insights regarding knowledge, attitudes and behaviours in Ireland towards generic medicines, determine and evaluate the internet resources likely to be accessed by those seeking knowledge on this topic across a number of English-speaking regions, and provide a unique tool to enhance the promotion and provision of relevant information. The outcomes of the research provide, I hope, a valuable resource to not only the many professionals working, globally, in the area of improvement of public health, but also to interested members of the general public.
Acknowledgements
To slightly paraphrase John Donne’s words: no woman is an island, and if I could compare this thesis to his allegorical continent, then there were many “pieces” that helped to form it into being; and without any of the individual “clods” that contributed, this continent would have been very much the less.

I would firstly like to thank Dr. Stephen Gallagher for rescuing me. I am grateful for your expertise, support, advice and unfailing good humour. To Prof. Ailish Hannigan and her statistical magic wand – your input into this work added a layer of depth and complexity that I would otherwise not have achieved – not the mention the invaluable advice and expertise from which both I and this thesis have benefited immeasurably; thank you so much. Thanks also to Prof. Mike Larvin and Dr. Huw Lewis who provided enormous support in tough times.

I would also like to express my gratitude to the Faculty of Education of Health Sciences for the fee-waiver scholarship that was granted to me. Again, without that support, this work might not have happened at all.

I am grateful to all the GPs, pharmacists and members of the general public who generously gave their time to take part in these studies – this work could, literally, not have existed without your input. I would also like to thank Dr. Pat O'Dwyer for permitting me to spend time in his surgery in Cappamore to recruit patients for these studies, and also to Dr. Mark Rowe, Cormac Johnston and all the staff in Waterford Health Park for similarly allowing me to spend time in their practice. Your generosity and commitment to scientific research in Ireland is laudable, and I am appreciative of it.
On a personal level, my little island could not have completed this work all on her own, and I am indebted to a lot of people who helped me along the way. To Dr. Niamh Cummins for her assistance – there’s nothing like having to explain your work to someone else to make sure you really understand it. To Jennifer Fitzgerald for going above and beyond and for admin support par excellence. To Lorraine Henry for her support and flexibility – you really helped to make this process so much easier for me. To Trisha, Tracy, Mary B, Natal, Clodagh, Nic P, Deb and all the other wimmen who were alongside me while all of this insanity was going on. Thank you all for listening (when I’m sure it was really boring) and for showing genuine interest in my research. I really appreciate it!

And of course to the best husband in the universe – Colum. The words “thank you” just don’t seem enough. You have supported, helped, advised, cajoled, encouraged, listened, discussed and always, always been there. I know that if I say “I could not have done this without you”, you will say that I could have; but know I would not have wanted to have done this without you. Honest. I love you more than I have words to say, and every day I am glad and grateful for your ever-present love and support (and so long as my thesis has more pages than yours, everything is right with the world). We’ll figure out where those commas belong as we go.

A wise person once said: hem your blessings with thankfulness so that they don’t unravel. I feel very blessed and hope that mine never disentangle.

Go raibh míle maith agaibh go léir.
Appendix 1

*Ethics Approval for the studies in Chapters 3 to 7.*
1st May 2012

Ms Suzanne Dunne
Graduate Entry Medical School
University College Limerick
Limerick

Attitudes, Beliefs and Behaviours towards Generic versus Proprietary Medicines in Ireland: A Cross Sectional Study Of Key Stakeholders

Dear Ms Dunne,

I wish to confirm that on review of the additional information received I am now happy to approve your study.

Yours Sincerely

Prof Colin Bradley
Chair Research Ethics Committee

(Original on file)
Appendix 2

Chapters, as published.
A review of the differences and similarities between generic drugs and their originator counterparts, including economic benefits associated with usage of generic medicines, using Ireland as a case study

Suzanne Dunne1*, Bill Shannon1, Colum Dunne1,2 and Walter Cullen1,2

Abstract

Generic medicines are those where patent protection has expired, and which may be produced by manufacturers other than the innovator company. Use of generic medicines has been increasing in recent years, primarily as a cost saving measure in healthcare provision. Generic medicines are typically 20 to 90% cheaper than originator equivalents. Our objective is to provide a high-level description of what generic medicines are and how they differ, at a regulatory and legislative level, from originator medicines. We describe the current and historical regulation of medicines in the world’s two main pharmaceutical markets, in addition to the similarities, as well as the differences, between generics and their originator equivalents including the reasons for the cost differences seen between originator and generic medicines. Ireland is currently poised to introduce generic substitution and reference pricing. This article refers to this situation as an exemplar of a national system on the cusp of significant health policy change, and specifically details Ireland’s history with usage of generic medicines and how the proposed changes could affect healthcare provision.

Keywords: Generic, Medicine, Drug, Pharmaceutical, Biosimilar, Prescribing, Healthcare, Economics, Ireland

Review

Summary Introduction: What are Generic Medicines?

Generic medicines are those where the original patent has expired and which may now be produced by manufacturers other than the original innovator (patent-holding) company. The term “generic drug” or “generic medicine” can have varying definitions in different markets, however the term is commonly understood, as defined by the World Health Organisation (WHO), to mean a pharmaceutical product which:

- is usually intended to be interchangeable with an innovator product,
- is manufactured without a licence from the innovator company, and
- is marketed after the expiry date of the patent or other exclusive rights [1].

There are differing legal requirements in different jurisdictions that define the specifics of what a generic medicine is. However, one of the main principles underpinning the safe and effective use of generic medicines is the concept of bioequivalence.

Bioequivalence has been defined as follows: two pharmaceutical products are bioequivalent if they are pharmaceutically equivalent and their bioavailabilities (rate and extent of availability) after administration in the same molar dose are similar to such a degree that their effects, with respect to both efficacy and safety, can be expected to be essentially the same. Pharmaceutical equivalence implies the same amount of the same active substance(s), in the same dosage form, for the same route
The purpose of establishing bioequivalence is to demonstrate equivalence between the generic medicine and the originator medicine in order to allow bridging of the pre-clinical and clinical testing performed on the originator drug.

The objective of this article is to provide an accessible resource describing the foundation of generic medicines, from their legal advent in the mid 1980’s to how current legislation and regulation of generics affects, inter alia, their composition, regulatory approval, pricing, and ultimately acceptance by healthcare professionals and patients. In this paper, we also focus on Ireland’s emerging policy on generic medicine use. Ireland is one of the EU ‘bail-out’ countries, and is attempting to conserve resources given the prevailing economic climate. Ireland is, therefore, currently poised to make the legislative changes necessary to introduce generic substitution and reference pricing in order to achieve reductions in the medicines bill for the state. This article refers this situation as an exemplar of a national system on the cusp of significant medical policy change, and specifically details Ireland’s history with usage of generic medicines and how the proposed changes could affect healthcare provision.

**Brief Comparison of Generic Medicines in the United States and Europe**

**Generic Medicines in the United States of America**

The US Food and Drug Administration [FDA], which regulates the pharmaceutical market in the United States [3] defines generic medicines as:

- a drug product that is comparable to brand/reference listed drug product in dosage form, strength, route of administration, quality and performance characteristics, and intended use [4]
- copies of brand-name drugs and are the same as those brand name drugs in dosage form, safety, strength, route of administration, quality, performance characteristics and intended use [5].

The 1984 Drug Price Competition and Patent Term Restoration Act (more commonly known as the Hatch-Waxman Act) in the US allowed for an abbreviated system for approval of generic copies of all drugs approved after 1962 [4], meaning that pre-clinical and clinical testing did not have to be repeated for generics [6]. The intended result of this legislation was to ensure that generic medicines would be less expensive than the equivalent originator medicine because it was not necessary for generic medicine manufacturers to repeat discovery, pre-clinical and clinical studies [7,8]. (It should be noted, as will be discussed later, that the cost of generics may vary considerably across countries depending on the specific active molecule involved, such that savings may not necessarily always accrue [9]). See Figure 1: Originator (New Drug Application - NDA) versus Generic (Abbreviated New Drug Application - ANDA) Review Process Requirements [8] for a comparison of the originator versus generic medicine review process.

To gain FDA approval, a generic medicine must:

- Contain the same active ingredient as the originator medicine (inactive ingredients may vary)
- be identical in strength, dosage form, and route of administration
- have the same use indications
- be bioequivalent
- meet the same batch requirements for identity, strength, purity, and quality
- be manufactured under the same strict standards of FDA’s good manufacturing practice regulations required for originator products [10].

Bioequivalence is demonstrated when the rate and extent of absorption do not show a significant difference from the originator drug, or where the extent of absorption does not show a significant difference and any difference in rate is intentional or not medically significant [4]. The FDA’s formal definition of bioequivalence is: the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site
of drug action when administered at the same molar dose under similar conditions in an appropriately designed study [11]. Therefore, bioequivalent drugs are pharmaceutical equivalents whose rate and extent of absorption are not statistically different when administrated to patients or subjects at the same molar dose under similar experimental conditions [12].

Currently, bioequivalence limits in use by the FDA when assessing a new generic medicine are that the generic medicine demonstrates 80-125% of the bioavailability of the originator drug [12]. In the US, the limit of 80-125% is unchanged for Narrow Therapeutic Range [NTR] drugs [12]. In other countries this is not the always case. In Australia, for example, there are no generic versions of digoxin or phenytoin [both having narrow therapeutic index and bioavailability problems] and, additionally, there are two brands of warfarin on the Australian market which are not considered interchangeable with each other – as no formal bioequivalence comparison of them has been made [2]. However, where branded warfarin was compared to bioequivalent generic formulations, similar outcomes for patients were observed, indicating that brand name warfarin was not superior to a generic alternative in a clinical setting [13].

The bioequivalence limits may suggest that a variance of 25% between an originator brand and a generic product is possible. However, this may not actually be the case. A study was performed which investigated 12 years of bioequivalence data submitted to the FDA, comparing the generic and originator measures from 2070 single-dose clinical bioequivalence studies of orally administered generic medicine products approved by the Food and Drug Administration (FDA) from 1996 to 2007. This study showed that the average difference in absorption into the body between the generic and the originator was 3.5% and is comparable to differences between two different batches of an originator drug [14]. However, it should be noted that variations between batches of originator drugs may themselves threaten patient safety. In 2012, Patel et al. reported that (in 2010) patients prescribed Lamotrigine (LTG, an anti-epileptic medication) experienced unexplained toxicity [15]. When investigated, the manufacturer (GlaxoSmithKline) accepted responsibility for an altered formulation due to changes made to the manufacturing process.

Generic Medicines in the European Union

The legal situation regarding authorisation of pharmaceutical products in the EU is more complex than in the US, with each member state having a competent authority in addition to the European Medicines Agency [EMA], which oversees EU-wide authorisation of medicines.

The EMA defines a generic medicine as: a medicine that is developed to be the same as a medicine that has already been authorised (the 'reference medicine'). A generic medicine contains the same active substance(s) as the reference medicine, and it is used at the same dose(s) to treat the same disease(s) as the reference medicine. However, the name of the medicine, its appearance (such as colour or shape) and its packaging can be different from those of the reference medicine [16].

Authorisation of a medicine in the EU can be done via three different routes: the Centralised Procedure [CP], the Decentralised Procedure [DCP] or the Mutual Recognition Procedure [MRP] [17]. Additionally, National Procedures [NP] are in place in individual member states, which allow a medicine to be authorised by the competent authority in that specific member state.

The CP, which came into operation in 1995, allows applicants to obtain a marketing authorisation that is valid throughout the EU. It is compulsory for medicinal products manufactured using biotechnological processes, for orphan medicinal products and for human medicine products containing a new active substance which was not authorised in the Community before 20 May 2004 (date of entry into force of Regulation (EC) No 726/2004) and which are intended for the treatment of AIDS, cancer, neurodegenerative disorder or diabetes. The centralised procedure is also mandatory for veterinary medicinal products intended primarily for use as performance enhancers in order to promote growth of treated animals or to increase yields from treated animals [18]. CP applications are made to, and approved by, the EMA.

To be eligible for the MRP, a medicinal product must have already received a marketing authorisation in one Member State. Since 1 January 1998, the MRP is compulsory for all medicinal products to be marketed in a Member State other than that in which they were first authorised. Any national marketing authorisation granted by an EU Member State's national authority can be used to support an application for its mutual recognition by other Member States [19]. The MRP is based on the principle of mutual recognition, by EU Member States, of their respective national marketing authorisations. An application for mutual recognition may be addressed to one or more Member States. The applications submitted must be identical and all Member States must be notified of them. As soon as one Member State decides to evaluate the medicinal product (at which point it becomes the "Reference Member State"), it notifies this decision to other Member States (which then become the "Concerned Member States") to whom applications have also been submitted. Concerned Member States will then suspend their own evaluations, and await the Reference Member State's decision on the product. This evaluation procedure - undertaken by the
Reference Member State - may take up to 210 days and, if successful, results in the granting of a marketing authorisation in that Member State. When the assessment is completed, copies of the report are sent to all Member States. The Concerned Member States then have 90 days to recognise the decision of the Reference Member State. National marketing authorizations are granted within 30 days after acknowledgement of the agreement [19].

The DCP is similar to the MRP but the difference lies in that it applies to medicinal products that have not received a marketing authorisation at the time of application. With the DCP, an identical application for marketing authorisation is submitted simultaneously to the competent authorities of the Reference Member State and of the Concerned Member States. At the end of the procedure, the product dossier, as proposed by the Reference Member State, is approved. The subsequent steps are identical to the mutual recognition procedure [20].

As in the US, applicants for a marketing authorisation [MA] for a generic medicine in the EU may submit an abbreviated application. According to Article 10(1) of Directive 2001/83/EC [21], an applicant for an authorisation to market a generic medicine is not required to provide the results of pre-clinical and clinical trials if it can be demonstrated that the medicinal product is:

A generic medicinal product or a similar biological medicinal product of a reference medicinal product, which has been authorised under Article 6 of Directive 2001/83/EC for not less than 8 years. This type of application refers to information that is contained in the dossier of the authorisation of the reference product. This information is generally not completely available in the public domain. Authorisations for generic or similar biological medicinal products are therefore linked to the ‘original’ authorisation. This does not however mean that withdrawal of the authorisation for the reference product leads to the withdrawal of the authorisation for the generic product (case C-223/01, AstraZeneca, judgment of the European Court of Justice of 16 October 2003). The generic or similar biological medicinal product, once authorised, can however only be placed on the market 10 or 11 years after the authorisation of the reference medicinal product, depending on the exclusivity period applicable for the reference medicinal product [22].

Generic medicine applications typically include chemical-pharmaceutical data and the results of bioequivalence studies, which demonstrate the similarity of the generic product relative to the reference medicine. As stated previously, the tolerance levels involved have been favourably compared to those acceptable for inter-batch variation during production of the originator medicine [14]. The authorising regulatory agency(ies) is referred to the data that were established in the originator product’s application for authorisation for information concerning the safety and efficacy of the active molecule. This is only possible once the data exclusivity period has expired on the originator product’s dossier [21,23]. The majority of authorizations for generic medicines are granted through the MRP and the DCP. Since the introduction of the DCP, the MRP has mainly been used for extending the existing marketing authorisation to other countries in what is known as the “repeat use” procedure [23].

EU bioequivalence parameters are similar to those mandated in the US, requiring that the test and reference products be contained within an acceptance interval of 80.00 – 125.00% of the AUC [area under the concentration time curve], which reflects the extent of exposure, or C_{max}, at a 90% confidence interval. European guidelines, however, also provide a tightened acceptance interval of 90.00-111.11% for narrow therapeutic index drugs [NTIDs] as well as different assessment requirements for highly variable drug products [HVDPs] [24].

Overall, both EU and US legislation for the authorisation of generic medicines allow for abbreviated applications to be made in the case of generic medicines. In both jurisdictions, pre-clinical and clinical studies do not have to be performed by the generic medicine applicant, but bioequivalence to the originator or “reference” medicine must be demonstrated. This abbreviated application process is often quoted as one of the main reasons for the price difference between generic and originator drugs. However, there is variation in generic medicine prices (e.g., within the single market European Union) unrelated to Research and Development expenditure and greatly influenced by local regulations and reimbursement arrangements that may, in some cases, be disassociated from the costs of manufacture and distribution [9]. Other important influencers include demand-side pressures (i.e., education, engineering, economics, and enforcement), International Nonproprietary Name (INN) prescribing, and, specifically, reference pricing which have been widely adopted by European governments [25-29]. It is also worth noting that generic medicine pricing is being driven further downwards as a result of keen competition in this sector. There is evidence of European generic medicine manufacturers facing competition from Indian producers, and a now-established practice of discounting prices to Governments [9,30]. Indeed, experts are now recommending that “European countries must continue learning from each other to fund increased volumes” and so exploit such discounts for bulk purchases [29]. As a result of these
and other factors, generic medicines are generally between 20 to 90% cheaper than their originator equivalents [31] which has obvious implications for healthcare costs. For example, in October 2010 in the UK, generic simvastatin (a cholesterol-lowering medicine) cost £1.12 for a pack of 28 (20mg) compared with approximately £30 for a pack of 28 (20mg) of the originator product [32].

**A Brief History of Pharmaceutical Regulations**

**Major Pharmaceutical Legislation in the United States of America**

Notable regulations published relating to pharmaceutical regulation in the 20th century began in 1906 with the Pure Drug and Cosmetic Act [PDCA] in the United States. In 1905, a book called *The Jungle* was published, in which Upton Sinclair wrote about the Chicago meat packing industry. The book described the unsanitary conditions in which animals were slaughtered and processed, including the practice of selling rotten or diseased meat to the public [33]. This book had a major impact on the American people and led the US Congress to pass the PDCA. With this new law, it became illegal to sell contaminated [adulterated] food or meat, and for the first time labelling of food and drugs had to be truthful – meaning that false or exaggerated claims could no longer be made on labels. The Act also required selected dangerous ingredients to be labelled on all drugs and inaccurate or false labelling was called “misbranding” and also became illegal.

The US Congress passed the Federal Food, Drug and Cosmetic Act [FDCA] in 1938 to complement the PDCA. This was largely in response to a public health disaster with a medicine called Elixir Sulfanilamide in 1937. Elixir Sulfanilamide was a sulfa drug sold as an anti-infective. Over 100 people died, most of them children, following ingestion of this medicine due to the fact that it contained diethylene glycol [DEG] as a solvent. DEG is a chemical analogue of antifreeze and is toxic to humans. The company that manufactured the medicine did not perform any toxicity testing prior to marketing the drug as, at the time, there were no regulations requiring the pre-marketing safety testing of new medicines. The FDCA required, *inter alia*, that new drugs be demonstrated as safe to humans before marketing [34].

The Public Health Service [PHS] Act, which was passed in 1944, was the legal basis for the licensing and gaining of marketing approval of biologic products [35]. Biological products are medicinal products that include vaccines, blood and blood components, allergens, somatic cells, gene therapy, tissues, and recombinant therapeutic proteins. Biologics can be composed of sugars, proteins, or nucleic acids or complex combinations of these substances, or may be living entities such as cells and tissues. Biologics are isolated from a variety of natural sources - human, animal, or microorganism - and may be produced by biotechnology methods and other cutting-edge technologies. Gene-based and cellular biologics, for example, are often at the forefront of biomedical research, and may be used to treat a variety of medical conditions for which no other treatments are available [36].

The 1962 Kefauver-Harris Drug Amendments [KHDA] added further protection to public health. The KHDA added the requirement that drugs be proven effective for their intended use. With both the 1938 and 1962 laws in place, US regulators were now ensuring that drugs made available to the American public were relatively safe to consume, in addition to being proven effective in treating the disease or condition that they were being marketed in relation to.

In response to the emerging AIDS crisis in the 1980's, the Orphan Drug Act [ODA] was enacted in 1983 to encourage the development of medicines for conditions that affected small populations by providing monetary and marketing incentives to drug manufacturers. The following year, in 1984, the US Congress also enacted the Hatch-Waxman Act [HWA], which provided for the marketing of generic medicines, the aim of which was to save Americans money on their medicine bills.

The Biologics Price Competition and Innovation Act of 2009 (BPCI Act) was signed into law, by President Barack Obama, on March 23, 2010. The BPCI Act was an amendment to the Public Health Service Act to create an abbreviated approval pathway for biological products that are demonstrated to be highly similar (biosimilar) to a Food and Drug Administration (FDA) approved biological product. This Act is similar, conceptually, to the Hatch-Waxman Act and it aligns with the FDA’s longstanding policy of permitting appropriate reliance on what is already known about a drug, thereby saving time and resources and avoiding unnecessary duplication of human or animal testing [37].

Other pieces of legislation have been, and continue to be, enacted to refine aspects of pharmaceutical manufacturing and good manufacturing practices, in addition to ensuring that modern scientific practices and developments are incorporated into law. Refer to Figure 2, History of Pharmaceutical Regulations – Timeline of Significant Legislations in the 20th and 21st Centuries, for a schematic timeline of the introduction of the major pieces of pharmaceutical regulatory legislation in the US and EU.

**Major Pharmaceutical Legislation in the European Union**

The first European pharmaceutical directive, 65/65/EEC, was brought into force on 26 January 1965 [38]. It aimed to establish and maintain a high level of protection for
public health and required prior approval for marketing of originator medicinal products. Much of the impetus behind Directive 65/65/EEC stemmed from determination to prevent a recurrence of the thalidomide disaster in the early 1960s, when thousands of babies were born with limb deformities as a result of their mothers taking thalidomide as a sedative during pregnancy. This experience, which shook public health authorities and the general public made it clear that, to safeguard public health, no medicinal product must ever again be marketed without prior authorization [39].


The Council adopted directives in 1992 on the wholesale distribution, classification for supply, labelling and packaging, and advertising of medicinal products for human use. The EU also introduced pharmacovigilance (the surveillance of the safety of a medicinal product during its life on the market), requiring Member States to establish national systems to collect and evaluate information on adverse reactions to medicinal products and to take appropriate action where necessary.

A new European system for authorising medicinal products came into effect in January 1995 (via Regulation EEC/2309/93 [42] & Directive 93/41/EEC [43]) along with the establishment of the new European Medicines Evaluation Agency. It offered two routes for authorising medicinal products: a "centralised" procedure, through the European Medicines Evaluation Agency (EMEA) (now the European Medicines Agency (EMA) [44]); and a "mutual recognition" procedure through which applications are made to the Member States selected by the applicant, and the procedure operates by mutual recognition of the national marketing authorisation. Additionally, updates to the requirements relating to the placing on the market of high-technology medicinal products, particularly those derived from biotechnology, were put in place.

The newest piece of major legislation in Europe is the Falsified Medicines Directive [2011/62/EU] [45], effective on 02 January 2013, which aims to protect European consumers against the threat of falsified medicines that might contain ingredients, including active ingredients, not indicated on the labelling, are of poor quality or are
in the incorrect dose – either too high or too low. As they have not been properly evaluated to check their quality, safety and efficacy they are potentially detrimental to public health and safety. The term ‘falsified’ is used to distinguish from the infringement of intellectual property rights, so-called ‘counterfeits’. As falsifications become more sophisticated, the risk that these products reach patients in the EU increases every year [46].

Biosimilars

The newest incarnation of off-patent medicines are “biosimilar” medicines, also known as “follow-on biologics”. Biosimilar medicines have been a reality in the European Union for several years and the necessary legal framework was adopted in the EU on 31 March 2004 with the first biosimilar medicines approved by the European Commission in April 2006 [47].

A biological medicine is a medicine whose active substance is made by or derived from a living organism. For example, insulin can be produced by a living organism (such as a bacterium or yeast) which has been genetically manipulated to produce insulin [48]. A “biosimilar” medicine is one that is similar to a medicine of biological origin that has already been authorised (known as the biological reference medicine). Biological products are fundamentally different from standard chemical products in terms of their complexity, and it is unlikely that the biosimilar product will have an identical structure to that of the reference product, thereby requiring evidence of safety and efficacy before approval. In this regard, biosimilars are different to the (to date) more familiar generics.

As with other generic medicines, a biosimilar medicine undergoes testing to ensure that it is as safe and effective as the reference product. However, due to the complex method of production, the active substance may differ slightly between the two medicines and so, additional safety and efficacy studies may be required on a case-by-case basis.

Since biosimilar and biological reference (originator) medicines are similar but not identical, the current recommendation is that the patient should be prescribed the same formulation (either the originator or biosimilar formulation) on each occasion [48]. See Table 1 Examples of Biosimilar Products (Adapted from [49]) for some examples of originator (i.e. reference) biologics and their biosimilars.

Drug Development

Development of new drugs is a complex and costly process. It generally takes 10–15 years, and studies have shown that it can cost between US$800 million to US$2 billion to get a new drug to market, with similar, or even higher, costs for development of biopharmaceuticals [biologics] [50].

Research and Development [R&D] involves discovery [preclinical studies] and development [clinical studies] of New Chemical Entities [NCEs] also known as New Molecular Entities [NMEs]. It is worth noting that of about 10,000 NCEs investigated to potentially treat a disease, only 250 might make it to animal testing and, of these, approximately 5–10 will qualify for testing in humans. Between 19 and 30% of Investigational New Drugs [INDs] that begin Phase 1 trials make it to marketing [51], meaning that only 1–2 of the original 10,000 NCEs will result in a marketable product.

An experimental medicine, also known as an Investigational Medicinal Product [IMP], is first tested in in vitro laboratory studies and in vivo animal studies. Following success here, the testing can move to the clinical phase where the IMP will be used for the first time in human clinical trial volunteers. Refer to Figure 3, Schematic of Drug Development Process (adapted from [52]), for an illustration of the process.

Naming of New Drugs

During the R&D process, a new pharmaceutical substance is given an International Non-proprietary Name [INN] or Generic name, in addition to the name that may eventually become its proprietary, or brand, name. Each INN is unique, globally recognised and is public property.

Non-proprietary names are intended for use in pharmacopoeias, labelling, product information, advertising and other promotional material, drug regulation and scientific literature, and as a basis for product names, e.g. for generics. Their use is normally required by national or, as in the case of the EU, by international legislation. As a result of ongoing collaboration, national names such as British Approved Names (BAN), Dénominations Communes Françaises (DCF), Japanese Adopted Names (JAN) and United States Accepted Names (USAN) are nowadays, with rare exceptions, identical to the INN. Names which are given the status of an INN are selected by the World Health Organisation on the advice of experts from the WHO Expert Advisory Panel on the International Pharmacopoeia and Pharmaceutical Preparations.

An important feature of the INN naming system is the use of a common “stem” which indicates the activity of the substance and the pharmacological group to which it belongs. The stem is generally placed at the end of the name, but in some cases it may be placed at the beginning or in the middle of the name. For example: substances having –adol/-adol- as the stem indicates an analgesic (e.g. tramadol); –mab indicates a monoclonal antibody (e.g. infliximab); -azepam indicates a diazepam derivative (e.g. temazepam) and –vir indicates antiviral
agents (e.g. acyclovir). All of the stems recommended by the WHO are contained in the “stem book” along with guidance for their use [53]. The INN, containing the common stem, provides a single, unique name which enables healthcare professionals to recognise the substance and the family of similar pharmacological substances to which it belongs. The INN is generally the name under which the generic from of a drug is marketed.

Pre-Clinical Research

The earliest stage of development of a new drug begins with the synthesis and purification of the new chemical moiety, or the screening of existing compounds for potential use as drugs. The aim of pre-clinical research is to determine whether the drug is reasonably safe for potential use in humans, and sufficiently effective against a disease target in chemical tests or animal models. During pre-clinical studies, the pharmacology of the new

![Figure 3 Schematic of Drug Development Process.](image-url)

Table 1 Examples of Biosimilar Products

<table>
<thead>
<tr>
<th>Reference biologic (active substance)</th>
<th>Manufacturer</th>
<th>Biosimilar products</th>
<th>Manufacturer</th>
<th>Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genotropin (somatropin)</td>
<td>Pfizer</td>
<td>Valtropin Omnitrope</td>
<td>BioPartners</td>
<td>Human Growth Hormone</td>
</tr>
<tr>
<td>Eprex (epoetin alpha)</td>
<td>Johnson &amp; Johnson</td>
<td>Retacrit (epoetin zeta)</td>
<td>Sandoz</td>
<td>Control of erythropoiesis</td>
</tr>
<tr>
<td>Neupogen (filgrastim)</td>
<td>Amgen</td>
<td>Tevagrastim</td>
<td>Teva Generics</td>
<td>Granulocyte colony-stimulating factor</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Filgrastim Hexal</td>
<td>Hexal AG</td>
<td></td>
</tr>
</tbody>
</table>

Table 1 Examples of Biosimilar Products

![Table 1](image-url)
drug in addition to its pharmacokinetics: absorption, distribution, metabolism, excretion & half-life; and pharmacodynamics: mechanism of action and estimates of therapeutic effects, are assessed. Initial studies relating to toxicology including carcinogenicity, mutagenicity, and teratogenicity are also carried out, as are efficacy studies on animals.

Clinical Trials
Once permission has been received from the appropriate regulator to administer a new drug to humans, clinical studies may commence. Clinical studies required to bring a new drug to market generally take place over three phases as follows:

- **Phase 1:** Safety studies on healthy volunteers. Typically involve 20–80 healthy volunteers (women of childbearing potential are excluded). The emphasis is on drug safety and on the building of a safety profile for the drug in humans.
- **Phase 2:** Clinical studies on a limited scale to determine efficacy of the drug. Typically involve 100–300 individuals who have the target illness. Patients receiving the drug are compared to similar patients receiving a placebo or another drug, and safety evaluations continue.
- **Phase 3:** Comparative studies on a large number of patients. Typically involve 1000–3000 patients. The emphasis is on safety and effectiveness and studies investigate different populations and different dosages as well as evaluating the new drug in combination with other drugs. Data gathered in a phase 3 trial are used to determine the risk versus benefit profile of the drug.

Following successful completion of clinical trials, the entirety of the information about the drug is compiled into an application and submitted to the relevant competent authority [e.g. FDA in the US, or EMA in Europe]. The competent authority reviews this application, and additional information may be sought from, or discussions held with, the applicant before the regulator makes its decision. The regulator will, after assessing the scientific data pertaining to the new drug, either allow it to be marketed, or deny approval to the applicant.

Registration
The next step in bringing a new medicine to market is the filing of an application with the health regulatory authority of a country in order to obtain approval to market the new medicine. This step is known as registration. In the US, a New Drug Application (NDA) or Biologic License Application (BLA) is filed with the US Food and Drug Administration (FDA). In Europe, a Marketing Authorization Application (MAA) is filed with the European Medicines Agency (EMA), or local competent authority, dependent on the approval route being used. A description of the medicine's manufacturing process along with quality data and trial results are provided to the health regulatory authorities in order to demonstrate the safety and effectiveness of the new medicine. If approval is granted, the new medicine can be marketed for use by patients.

Post-Marketing Surveillance
Post-market surveillance studies [also called Phase 4 trials] of the drug continually assess the safety of the drug in the marketplace. This may include reporting and investigation of the incidence and severity of rare adverse reactions, cost-effectiveness analyses, comparative trials, and quality of life studies.

Where Do Generic Medicines Fit Into This Process?
Applications for marketing approval of generic medicines [i.e. the submission of an ANDA in the US, or a generic MAA in Europe] are made at approximately the same time point as the registration step for originator (i.e. proprietary) medicines. Generic medicine applications do not need to contain the pre-clinical and clinical studies required for originator medicines, with relatively simple bioequivalence studies being acceptable in their place, as discussed earlier [8,16].

Referring to Figure 3, it can be seen that the difference in the cost of generic medicines is primarily due to the fact that investment in generics is significantly less than for new originator medicines. Without the need to recoup the costs of pre-clinical and clinical studies, generic manufacturers can price their product lower than the originator product. However, as referred to previously, the market price of the product can be considerably influenced by end-user and prescriber perception, local regulations and reimbursement models [9].

From a production point of view, however, the cost of manufacturing an originator or a generic will probably not differ significantly as they are both manufactured under the same industry standards and conditions. In fact, it is not uncommon for the manufacturer of an originator product to become a manufacturer of a generic version of the drug, once the patent for the drug has expired and it becomes open to generic competition [2]. From an economic perspective, this allows the company to continue recouping the cost of their capital and R&D investment from first introducing the product to the market.

Are Generic Medicines Really The Same As The Originator Medicines?
It has been clearly shown that, at least at a physiological level, generic medicines behave very similarly to their
originator counterparts. As described earlier, an assessment of 12 years of bioequivalence data submitted to the FDA, comparing 2070 single-dose clinical bioequivalence studies of orally administered generic medicine products approved by the Food and Drug Administration (FDA) from 1996 to 2007, demonstrated that the products did not differ significantly [14]. Similarly, referring to clinical efficacy, Kesselheim et al. (2008) published an extensive systematic review and meta-analysis (referred to previously) that were favourable towards use of generic drugs in treating cardiovascular disease [13]. In another study they reported that, for anticonvulsant drugs, "evidence does not suggest an association between loss of seizure control and generic substitution" [54]. Further, many studies have demonstrated that initiation of treatment with generic medicines or switching to generic medicines are not associated with poorer patient outcomes. Specifically, Amit et al. in 2004 showed that a generic formulation of propafenone, used to treat atrial fibrillation, was found to be at least as safe as the originator drug [55]. Additional evidence of safety in use of generic antipsychotic medicines was provided by Araszkiewicz et al. [56] while the safety and efficacy associated with switching of drugs was has also been positively reported [57,58].

Researchers have, however, also reported patient concerns related to generic medicines. These studies range from qualitative assessment of perceptions in specific patient cohorts [59] to general lay/consumer knowledge [60,61], versus knowledge of professionals [62,63]. Many of these studies focus on the influence of relative cheapness on perceptions and use of generic medicines [64,65]. Some publications have shown that consumers felt that a generic medicine did not work either as effectively, or at all, in comparison to when they were taking the originator medicine [66]. For example, reports from patients show that symptoms of depression, which returned while taking a generic medicine, abated again when they switched back to the originator medication [66]. Researchers investigating the efficacy of generic bisphosphonates in the management of osteoporosis demonstrated that they resulted in poorer increases in bone mineral density than branded products [67] and postulated that reasons for this may include higher levels of gastrointestinal adverse events and poor tolerance of generic formulations associated with an increased likelihood of generic particulate matter adhering to esophageal mucosa [68]. However, newly recommended criteria for the evaluation of treatment failure in osteoporosis may stimulate further research into this clinical challenge [69].

In treatment of epilepsy, significant problems have been reported, including breakthrough seizures and increased side effects following a switch to a generic antiepileptic drug [AED] [70]. Additionally, Jain (1993) ascertained that 26 of 131 cases of carbamazepine failure reported to the drug maker were associated with seizure increases following a switch to a generic formulation. Seizure control returned to baseline when the brand formulation was reinstituted [71]. Mayer et al. (1999) compared patients who were receiving a generic extended-release carbamazepine formulation with patients taking a branded formulation, in an unblinded trial, and found that 9 of 13 subjects experienced adverse effects when on the generic formulation, with AUC fluctuations that are acceptable within current FDA guidelines [72]. It can be concluded, therefore, that at least in the case of AEDs, bioequivalence, as defined in regulations, does not always correspond to therapeutic equivalence because of the permitted range, evaluation methods and individual variation [73], although this has been refuted in an extensive meta-analysis by Keselheim et al. [54] who found that generic substitution had no impact on efficacy of seizure control.

Incidence such as those described above have resulted in caution being expressed by professionals regarding the safety and effectiveness of generic medicines, albeit in a minority of situations [74,75]. This is contrary to the fact that there is strong evidence that consumers believe that generics are less expensive (and therefore better value) than brand-name drugs, and are as safe [76]. Indeed, the debate is further fuelled by incisive systematic reviews of the published literature. For example, Talati et al. (2012) assessed the efficacy, tolerability, and safety of innovator versus generic antiepileptic drugs, and demonstrated that (albeit with a low strength of evidence) initiating treatment with an innovator or generic antiepileptic drug will provide similar efficacy, tolerability, and safety but that switching from one form of medication to the other may be associated with more hospitalizations and longer hospital stays [77]. Some experts have stated that switching between originator and generic drugs may actually be unethical, raise the cost of treatment, with additional clinic visits and laboratory tests [78,79]. Similar arguments are made when addressing the concept of therapeutic substitution, whereby there may be an attractive price differential between established drugs whose patents have expired and for which generics are available and newer (or branded) medicines within the same therapeutic class, as researchers have made the point that direct evidence to support equivalence may be lacking [80-82].

While the active pharmaceutical ingredient (API) does not differ between originator and generic medicines, other (inactive) ingredients, known as excipients, may be different and a number of pharmaceutical excipients are known to have side effects or contraindications [83]. As excipients may differ between originator medicines and generic preparations which have been shown to be
bioequivalent and therefore substitutable, there needs to be an awareness in the medical/healthcare community that where a generic preparation contains an excipient which is not part of the originator preparation, there is the potential for the generic formulation to cause problems in a patient who had no issues in tolerating the original preparation.

Evidence has been published that differences in excipients between originator medications and their generic counterparts can cause problems. For example, allergic reaction has been reported to croscarmellose sodium used as excipient in a generic furosemide preparation in a patient who had previously been taking branded furosemide without incident [84]. (Croscarmellose is used in injectable preparations as a suspending agent to promote solubilization of compounds with poor water solubility; it is also present in tablets as binder, glidant and antiadherent).

Similarly, a lactose-intolerant patient with an arrhythmia who is switched from one formulation of antiarrhythmic drug to another that contains a lactose-based excipient may experience gastrointestinal disturbances which could affect gut transport time and overall drug absorption, thereby affecting systemic levels of the drug [85]. Studies have also reported significantly different serum levels of antiarrhythmic drugs associated with originator products and their generic equivalents, in addition to observing patients’ symptoms recur following a switch to a generic formulation. These observations have led to the conclusion that there is evidence that formulation substitution in the cardiovascular arena has risks [85].

More broadly, allergies to excipients contained in topical steroids have also been well documented [86] - with these allergens being contained in both originator and generic preparations. Saccharose, an excipient with potential side effects, was seen in generic preparations of phenobarbitol used to treat epilepsy in Mauritania [87]. Lactose and saccharose are contraindicated in people with lactase or saccharase deficiencies and as the frequency of these enzyme disorders is high in African populations [88], this suggests the potential for negative clinical reaction to such medicines in African patients.

Therefore, while bioequivalence between an originator medicine and a generic equivalent may have been proven, as required by the current regulatory guidelines, given the differences in other ingredients it is incumbent on prescribing physicians to remain vigilant to the potential risks, and exercise caution in the substitution of a medication with an equivalent. This is applicable to both substitution of a branded medication with a generic equivalent and to switching between different, equivalent, preparations of generic medications (e.g. the same generic medication produced by different manufacturers).

This, however, is not an effect limited to use of generic medicines. As described earlier, Patel et al. reported that (in 2010) patients prescribed an anti epileptic medication experienced unexplained toxicity [15] which, when investigated, was found to be due to altered formulation. Despite this, regulators have, in some cases, adopted a cautious approach in legislating for potential risks associated with generic substitution, in particular possible challenges relating to continued efficacy and safety of treatment under defined circumstances. In July 2011, the Danish Government banned generic substitution for immunosuppressants (specifically, cyclosporine and tacrolimus) due to issues relating to the possible need for increased testing requirements following use of generics in transplant patients [89]. Similarly, the British National Formulary (BNF) currently recommends brand prescribing for a number of medicines and drug classes, namely modified release diltiazem [90 p132]) and cyclosporine [90 p583], while in July 2008 the Northern Ireland Health and Social Care Board issued an extensive list of medicines considered unsuitable for generic prescribing [91] which included narrow therapeutic index drugs, modified release preparations, controlled drugs including patches, inhalers, and multi-ingredient products.

Usage of Generic Medicines in Ireland, a Case Study
Irish healthcare spending in 2010 accounted for 9.2% of GDP [92], with total expenditure on pharmaceuticals amounting to €2.2 billion, and public expenditure on pharmaceuticals (administered by the Primary Care Reimbursement Service, PCRS) amounting to €1.9 billion. Public expenditure on pharmaceuticals was one of the fastest growing components of public health expenditure over the period 2000 to 2010. It increased by 158.5 per cent in real terms and accounted for 12.9 per cent of total public health expenditure in 2010 (up from 10.1 per cent in 2000) [92].

State assistance towards the cost of pharmaceuticals is available under a number of different schemes. The General Medical Services (GMS, or medical card) Scheme provides free public health care (including GP care and prescription pharmaceuticals) to those who satisfy an income means test. In April 2011, over 1.6 million individuals had a medical card, accounting for 36.2 per cent of the population. A further 2.6 per cent of the population were eligible for free GP services (but not prescription pharmaceuticals) under the GMS Scheme (known as GP Visit card holders) [93]. Non-medical cardholders avail of State assistance towards the cost of prescribed pharmaceuticals under a number of Community Drugs Schemes (CDS). The three largest (in expenditure terms) are the Drugs Payment (DP), Long Term Illness (LTI) and High Tech Drug (HTD) schemes. At the time of
writing, all those ineligible for a medical card were eligible for the DP Scheme, whereby the State pays the full cost of prescription pharmaceuticals and certain appliances above a monthly threshold of €132 per family.

Penetration of generic medicines into the Irish market is amongst the lowest in Europe. See Figure 4: Market Shares (By Volume) of Generic Medicines in Europe in 2006 (data from [94]). Furthermore, in a report written by the NCPE for the Irish Department of Health and Children (DOHC) in 2008 it was reported that generic prescribing in Ireland had fallen from over 22% by volume in 1997, to just over 19% in 2007 [93]. As a result of this poor penetration by generic medicines, Irish expenditure per 1000 inhabitants per annum is ten times that of Sweden, putting in perspective the considerable need to quickly realize the substantial savings that are possible without compromising patient safety or efficacy of treatment.

In 2008, approximately a quarter of all prescriptions dispensed on the GMS, DP and LTI schemes had an available generic equivalent [95]. That translated into €227.76 million which was spent on originator medicines where there was an equivalent, less expensive, generic product available representing a potential area for cost saving to the Irish state. Moreover, from the NCPE’s 2008 figures, an immediate opportunity for increase in use of generics in Ireland can easily be seen, as the DP/LTI figures show a difference of 7% in the proportion of prescriptions that were for generics compared to generic prescriptions from the GMS [96].

Cost-Saving Potential in Ireland
The net cost of the Irish Community Drug Schemes more than doubled in a seven year period, from €1.024 billion in 2001 to more than €2.289 billion in 2007 [96]. The increase is partly explained by a "low" price fixed in 1992, subsequently renegotiated, and 50% mark-up (on ingredient costs) and dispensing fees agreed with dispensing pharmacists in parallel with an ageing population accessing the GMS scheme. The four schemes together account for 98% of prescriptions and 99% of expenditure in the community setting [97].

Cost-saving opportunities, including something as straightforward as closing that 7% difference between GMS and DP/LTI generic prescription figures, may be critical to the Irish state, in an era when healthcare costs are escalating. Furthermore, it was reported in 2003 that there was the potential for 40% of medicines prescribed on the GMS to be dispensed generically [98]. As increasing numbers of originator medicines reach the end of their patent/exclusivity periods, thereby allowing generic competitors to enter the market, this area represents an increasing potential for cost savings for the public purse.

Total expenditure on originator medicines in Ireland rose from €120 million in 2004 to more than €220 million in 2008 [99]. In 1997, the average cost per dispensed item under the GMS scheme was €11.20 as compared with €23.27 in 2007. Factors contributing to the increase in drug expenditure include the “product mix” (the prescribing of newer, more expensive medications) and the “volume effect” (comprising of the growth

Figure 4 Market Shares (By Volume) of Generic Medicines in Europe in 2006 (reproduced with permission from the European Generic Medicines Association).
in the number of prescription items issued). In 1997, twenty million prescription items were issued under the GMS scheme. This increased over two-fold to 44.35 million items in 2007. The year on year increase in pharmaceutical expenditure in Ireland is amongst the highest in Europe with medicines, in 2009, accounting for approximately 13.5% of total healthcare spending [100].

Healthcare costs, as previously demonstrated, may be somewhat mitigated by increased prescription of generic medicines. It has been recommended that the State examine the price it pays for generic medications and encourage greater INN prescribing by doctors [95]. In recent years, a trend towards the prescription of generic medicines has been seen worldwide. For example: in the US, in 1984, only 14% of prescriptions were for generic medicines. This had increased to 66% in 2006 [95] and by 2011 78% prescriptions written in the US were for a generic medicine [8]. In the UK, generic medicines accounted for approximately 83% of all prescriptions written in 2009 and 2010 [101]. [That rate, incidentally, is generally considered to be in the region of the maximum expected rate of generic prescribing]. A key driver for such a high rate of generic prescribing has been the training of UK physicians to prescribe by INN where possible, something which is subsequently continued and encouraged in practice [102] and is one of multiple initiatives used in Scotland with particular emphasis on PPIs and statins [103]. It is worth noting that in Ireland, in 2007, generic prescribing comprised 2.6% unbranded generics versus 16.4% branded generics (78) and is, thus, a target for education regarding generic usage. Indeed, a related aspect of branded versus unbranded generic prescribing is that there is evidence of confusion where patients are dispensed a different branded generic on each pharmacy visit, resulting in pharmacist (and, presumably, physician) resources being invested in explaining to the patient that their new drug is the same as the previous one [104]. A lesson for Ireland may be that such patient confusion could be avoided if related education of patients is introduced with implementation of the new policy.

An increase in use of generics is associated with significant cost savings, for example in 2010 alone, the use of generics in the American health system saved $158 billion, an average of $3 billion every week [25] and a study by the Generic Pharmaceutical Association (GPhA) showed that prescribing of generics has saved the US economy $931 billion between 2001 and 2010 [105].

In mid 2010, the Irish Minister for Health announced plans to introduce new legislation to allow the introduction of reference pricing and to permit generic substitution/medicine interchangeability in Ireland. A report entitled the Proposed Model for Reference Pricing and Generic Substitution, which describes the model to be implemented in Ireland, indicates the reason for the proposed changes:

**Reference Pricing & Generic Substitution**

With reference pricing, a common reimbursement price or reference price, is set for a group of interchangeable medicines based on the price of a “reference drug” which is chosen from that group of drugs [25,103]. The reference drug will be as safe and effective as the other available drugs in the group and may or may not be a generic medicine. The price of this reference drug is the price paid by the State, and if the patient/customer wishes to have a different, more expensive, drug to the reference drug, they must pay the difference in price themselves [107]. Provision is generally made for prescribers to prohibit substitution for clinical reasons. In these instances, patients do not face any additional costs if the prescribed product costs more than the reference price.

At the time of writing, neither generic substitution nor reference pricing are permitted in Ireland despite being used in many other countries both in Europe and elsewhere. In these countries, the pharmacist can substitute medicines that have been designated as interchangeable – that is: a medicine of the same quality and clinical efficacy, but of a lower cost, can be dispensed in place of what was prescribed.

However, despite evident success in a number of countries, it has been argued that additional savings may be possible without impacting the continued efficacy or
safety of patient treatment. A 2007 study by Kanavos [108] reported that the UK National Health Service was reimbursing for generic medicines at too high a price, and that a considerable proportion of the reimbursed price accrued to the distribution chain in a fashion that resembles standard retail models. Indeed, it was claimed that this overpayment effectively constituted a subsidy to pharmacists (intended or otherwise). Analogous over-payments were reported in a study of pharmacy discounts in France [109] where control of pharmaceutical expenditure has been a national policy priority for many years and health system measures have included reference pricing, generic substitution and international non-proprietary name (INN) prescribing. However, as in other markets, generic manufacturers and wholesalers offer discounts, rebates or promotions to pharmacies to gain an advantage over competitors, meaning that health insurance in France may be overpaying for generic medicines. As Ireland moves towards a formalized generic medicine policy, an opportunity presents itself to ensure the reimbursement costs are close to market price (including savings associated with volume discounts referred to earlier) and that the benefits of the new policy do not accrue disproportionately to the pharmacists and their wholesalers and medicine distributors.

Concerns
While the main objective for the introduction of generic substitution and reference pricing is to reduce costs related to healthcare for both the consumer and the State, the concept of reference pricing is not without its concerns.

The Irish Pharmacy Union (IPU) warned that reference pricing could lead to shortages of medicines and the Irish Pharmaceutical Healthcare Association (IPHA) stated that Ireland currently has a fair and equitable single-tier system whereby all patients, regardless of income, have access to secure supply of the medicines which their doctors believe are most suitable for them [110,111]. The IPU and IPHA believe that should the Health Services Executive [HSE] set the reference price at that offered by the lowest potential supplier, it could give rise to patients being dependent on one supplier, which could, perhaps, have very limited infrastructure or commitment to the Irish market. This, however, seems at odds with the market situation whereby smaller countries (such as Lithuania which has a population comparable to Ireland) obtain sufficient supplies of products including generic medicines at considerably reduced prices [112] and may, actually, represent an aversion to erosion of profits rather than accurately reflecting the market.

Concerns have also been expressed by organisations such as the Irish Medical Organisation (IMO) and Irish College of General Practitioners (ICGP). During a working group meeting held in January of 2010, the ICGP cautioned that switching of medicines may not be suitable and also that when determining which products are substitutable “the tests of bioequivalence must be robust” [113]. This point regarding equivalence is, as referred to previously, equally relevant to variability between successive batches of originator or generic products.

Acceptance of INN prescribing and Substitution by Prescribers in Other Countries
When generic substitution was first introduced in Australia (the Brand Substitution Policy (BSP); introduced in December 1994 [114]), two studies were conducted exploring medical practitioners’ views on generic medicines and generic substitution. The first study, conducted in 1995, five months after the government permitted generic substitution by pharmacists, was a national telephone survey of GPs. Out of a total of 71 GPs, 28 (39%) said ‘no’ to generics substitution, 22 (31%) said ‘yes’ to substitution and 21 (30%) were ambivalent [115]. The most common reason cited by those opposed to generics prescribing and substitution was that it would cause confusion among patients, particularly the elderly, because generic brands were often of different colours and shapes. (This argument ignores the fact that packaging and presentation of originator medicines may also differ depending on country of origin if sourced via parallel importation). Other reasons given were that it was a doctor’s responsibility, not a pharmacist’s, to decide on medication and that using generics meant less money for research. There were also concerns about bioavailability, adverse reactions to generics and the need for a free enterprise environment [115]. Despite presumably greater familiarity with generic medicines, similar views were expressed by some of the doctors in the second study, which was conducted in 2002 [115].

Analogously, in Sweden, researchers saw that while generic substitution was implemented in 2002, only 60% of the possible indicated savings were made in the first year, due somewhat to the mix of generic and originator products stocked by pharmacists [116]. Subsequent studies by Anderssen et al. showed that gender and age influenced Swedish patients’ generic medicine use [117] and further documented rational use of generic medicines through the establishment of drug and therapeutic committees, development of guidelines, academic detailing, continuous benchmarking of prescribing patterns and financial incentives that have led to effective implementation of a generic medicine policy by stakeholders recognizing the need to conserve resources [118].

In the US, individual physicians have expressed strong opinions about generic medicines over the years, with opponents of their use generally being more vocal.
1997, Banahan and Kolassa [119,120] reported a comprehensive analysis of physicians’ attitudes toward generic medications, finding that overall, physicians’ attitudes toward generic medicines were fairly neutral, as indicated by their answers to two key questions from their nationwide survey. In a separate study (from 2001), respondents expressed modest support for generic substitution, but had doubts about originator-generic equivalence [121]. More recently, Shrank et al. have reported studies addressing the relationship between generic medicine prescribing and physician practice location and specialty (i.e. higher income catchment areas equated to higher generic prescribing rates and generalist physicians prescribed more generic medicines than specialist physicians) [122]. Shrank et al. have also shown that persistence in generic medicine use is higher than with branded products in those patients benefiting from incentives offered by medical insurance companies and pharmacy drug purchase plans [123]. Perhaps most interesting is that, in 2012, Shrank et al. found that a meaningful proportion of physicians expressed negative perceptions about generic medications, representing a potential barrier to generic use. The researchers recommended that policymakers trying to encourage generic use should consider educational campaigns targeting older physicians [123].

Similar results were seen in a study carried out amongst Irish prescribers in 1997, which showed that the majority of prescribers were concerned about the reliability and quality of generic medicines [75], and the study concluded that education of stakeholders would be necessary to improve the level of INN prescribing in Ireland. An additional survey in 1997 indicated that over a third of Irish GPs believed that generic medicines were unreliable and of poor quality and 50% of pharmacists believed that some generic medicines were unreliable [124].

The United Kingdom consistently has higher rates of generic prescription than Ireland, and this is generally thought to be due to the fact that Government policy in the UK actively promotes INN prescribing from medical education to subsequent ongoing practice (as described earlier) through processes of monitoring or prescribing of generic versus originator/patented products. The introduction of fundholding practices provided further encouragement from a financial perspective [125], whereby medical practitioners’ fixed budgets provided an explicit incentive to contain costs, which in turn encouraged INN prescribing.

Previous Attempt at Improvement of Use of Generic Medicines in the General Medical Services Scheme in Ireland

In 1993, a drug budgeting arrangement called the Indicative Drug Target Savings Scheme [IDTSS] (also referred to as the Indicative Drug Budgeting Scheme) was introduced in Ireland as a result of a voluntary agreement entered into with the Irish Medical Organisation and the Department of Health [124]. The purpose of this scheme was to curtail spiraling GMS prescription costs by encouraging rational and cost-effective prescribing [125,126]. With this agreement, an annual “indicative drug budget” was calculated for each participating GMS GP, based on a combination of the doctor’s previous prescribing costs and the national average [126].

Typically, 50% of any savings made on these indicative drug budgets, achieved primarily through use of increased prescribing of generic medicines, were returned to the prescribing physician [127]. All savings had to be invested in the development of the general practitioner’s own practice. There were no penalties for overspending.

A report reviewing the IDTSS in 1997 indicated that the scheme saved IR£13.5 million [i.e. €17.14 million] during 1993–1994 [128]. Additionally, it showed that even those prescribers who exhibited lower-cost and fewer-item prescribing per patient, prior to implementation of the scheme, were successful in reducing their cost per item further through increased use of generic prescriptions [125]. The main conclusions from this report included that there were changes in prescribing behaviours, seen as enhanced prescribing of generic medicines, leading to lower drug costs per patient. Also, there were no discernible negative effects on overall quality of prescribing observed.

A study of the IDTSS by Walley et al. showed that the IDTSS encouraged changes in prescribing practice among low and medium cost prescribers, but had no apparent effect in higher cost prescribers. The changes were relatively short-lived with a similar rate of rise of costs across all groups by the third year of the scheme (1996) [125]. This is broadly similar to the effects of GP fundholding in the UK, where new fundholders dramatically reduced their prescribing costs, but where there were similar rates of rise of prescribing costs after 2–4 years in both fundholding and non-fundholding practices [127].

Despite the reported savings in the first year of the scheme [IR£13.5 million in 1994 [129]], the scheme was not entirely successful; 27% of GPs never achieved any savings in the first 4 years of the scheme [125]. Since December 2005, however, a freeze was placed on this scheme [127]. This may have a factor in the previously mentioned fall in prescribing of generic medicines seen between 1997 and 2008 in Ireland.

Conclusions

While acceptance of the definition of a generic medicine is ostensibly similar worldwide, there are some discrepancies between different jurisdictions, particularly related to determination of bioequivalence. For example,
Narrow Therapeutic Index drugs have distinct and different bioequivalence acceptability in the EU that is not in place in the US [126]. Differences such as this, in addition to the fact that components of a generic medicine [with the exception of the API], the appearance of the medicine and its packaging, can differ between apparently equivalent originator and generic medicines have led to publication of reports describing variability in efficacy and adverse events [130]. However, in a balanced debate, these studies and expressions of distrust should be evaluated alongside the many reports that have demonstrated comparable effectiveness and acceptability between generic and originator medicines [66,67,74,75].

Researchers have explored the attitudes and beliefs of stakeholders in the medicines process (that is: prescribers, dispensing pharmacists and patients/end users) demonstrating a spectrum of perceptions and opinion which are influenced by factors such as geography, age and demographics [54-56]. This information clearly demonstrates that if countries are to take advantage of the apparent economic benefits associated with generic medicine use, at least some of their “demand side” [118] activities should focus on education and enforcement to address the excessively sceptical perception of these products. Such approaches to enhance adoption of generic medicines should also be complemented by in-depth analysis of the potential disadvantages of generic products, such as potential variation in quality and formulation [25-29] and associated effects. However, it is probable that existing pharmacovigilence/surveillance systems, which are in place for all human medicines, will be sufficient for monitoring of these. It cannot, however, be disputed that the reputation and perception of reliability of generics needs improvement in the eyes of those healthcare professionals and patients who have articulated poor opinions of them.

The economic benefits of the use of generic medicines cannot be denied; and in many countries their use is essential to control healthcare spending. Given that the majority of patient-doctor encounters result in the writing of a prescription [131], the cost of the medicine prescribed is of interest both to the patient/consumer and the State. The potential cost savings associated with the use of generic medicines must be considered by the bill-payers. In this paper, we have focused on Ireland’s emerging policy on generic medicine use. With Ireland now poised to make the legislative changes required in order to take advantage of generic substitution and reference pricing, the onus is on Ireland’s Health Service Executive, as well as the prescribers and dispensers of medicines, to ensure that they are fully informed of all the complexities associated with the use of generic medicines.

It is also important to learn from lessons of the past and to take into account previous attempts at increasing prescription rates of generic medicines in Ireland, such as the Indicative Drug Target Savings Scheme [IDTSS], as described earlier. Additionally, the Irish government and policy makers may find it useful to look at how generic substitution was successfully implemented in other countries and to take advantage of the depth of information and research available from other jurisdictions which have previously adopted generic substitution and reference pricing. It is in the best interests of the Irish healthcare system for its leaders to learn from the successes and challenges that have already been experienced by other countries such as the UK, France, Germany, Sweden and Lithuania, amongst others. In doing so, education of all stakeholders, including physicians and allied professionals and, in particular, end-users will be pivotal for the appropriate implementation and acceptance of policies for generic substitution/medicine-interchangeability and reference pricing in Ireland.

With many medicines hitting the so called “patent cliff”, generic drug usage, already trending upwards, is likely to continue to increase in the coming years, with generic medicines now being, primarily for economic reasons, a reality of modern healthcare systems.

Endnotes

“For the purposes of this article, the terms “generic drug” and “generic medicine” are considered interchangeable, and therefore, for simplicity of language, only the term “generic medicine” is used throughout.

Competing interests

The authors declare that they have no competing interests.

Authors’ contributions

SD researched and wrote this review. WC, BS and CD provided guidance, critical review and revision of the manuscript. All authors read and approved the final manuscript.

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Page 19 of 18

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doi:10.1186/2050-6511-14-1

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Physician and pharmacist perceptions of generic medicines:
What they think and how they differ

Suzanne Dunne*, Bill Shannon, Ailish Hannigan, Colum Dunne, Walter Cullen

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Beliefs, perceptions and behaviours of GPs towards generic medicines

Suzanne S Dunne, Bill Shannon, Walter Cullen and Colum P Dunne

http://dx.doi.org/10.1093/fampra/cmu024
Perceptions and Attitudes of Community Pharmacists Towards Generic Medicines

Suzanne S. Dunne, BSc (Hons), MSc; Bill Shannon, MD, FRCGP, MICGP; Walter Cullen, MD, MICGP, MRCGP; and Colum P. Dunne, BSc (Hons), MBA, PhD

ABSTRACT

BACKGROUND: Following the enactment of legislation in June 2013, generic substitution and reference pricing of medicines has been introduced, for the first time, in Ireland. This novel study is the first assessment of the perceptions of community pharmacists in Ireland towards generic medicines completed in the period immediately prior to the introduction of generic substitution and reference pricing.

OBJECTIVE: To determine the perceptions towards generic medicines among community pharmacists.

METHODS: One-to-one semistructured interviews were performed with a convenience sample of 44 community pharmacists (from approximately 4,500 pharmacists in Ireland) recruited from Ireland’s Midwest, South, and Southwest regions. Interviews were transcribed and analysed using NVivo (version 9).

RESULTS: 98% of pharmacists believed that generics were of a similar quality to the originator, and 96% stated that they were as effective as the originator. However, a small number demonstrated some reticence regarding generics: 9% believed that generics were not manufactured to the same quality as the originator; 7% stated they would prefer to take an originator medicine themselves; and 7% reported having experienced quality issues with generic medicines. 89% of pharmacists reported receiving patient complaints regarding use of generic medicine, although 64% suggested that this was due to a nocebo effect (i.e., a result of patients’ preconceived notions that generics were inferior). Only a minority (21%) reported that they had attempted to educate patients as to the equivalency of generics. Although 80% were in favor of Ireland’s new legislation promoting the use generic medicines, 64% suggested that this was due to a nocebo effect (i.e., a result of patients’ preconceived notions that generics were inferior). Only a minority (21%) reported that they had attempted to educate patients as to the equivalency of generics. Although 80% were in favor of Ireland’s new legislation promoting the use generic medicines, 64% expressed concerns regarding its practical implementation.

CONCLUSIONS: This key stakeholder group had positive attitudes towards generics and the legislation that promotes their use. Concerns regarding patient perception and experience, clinical effectiveness, and manufacturing quality were identified. We propose that interventions supporting implementation of the new legislation should address these concerns.

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What is already known about this subject

• Pharmacist perceptions of, and attitudes towards, generic medicines are a relatively unexplored area internationally, with only 10 publications found in PubMed on this topic since 2003.
• No studies of the views of community pharmacists in Ireland towards generic medicines have ever been published.

What this study adds

• This is the first study of pharmacist perceptions of generic medicines in Ireland and 1 of only 6 other studies on pharmacist perceptions of generics in Europe.
• This is only the second qualitative investigation of pharmacist views in Europe—the other being from Sweden and published in 2012.
• This study adds to the body of knowledge on pharmacist attitudes towards generics, providing in-depth, qualitative data that can be used as a basis for policy implementation and decision making.

In June 2013, new legislation came into effect in Ireland— the Health (Pricing and Supply of Medical Goods) Act 2013—that introduced generic substitution and reference pricing for the first time in this country. As a result of this new legislation, Irish patients will now have a greater opportunity to receive a generic medicine instead of a brand-name prescription medication. In an effort to ensure that this legislation is successful, pharmacists’ opinions of, and attitudes towards, generic medicines are critical to the changes being implemented—that is, to increase the use of generic medicines in Ireland.

Attitudes of Irish pharmacists towards generics have not been published in the past. While assessments of pharmacist perceptions of generic medicines have been carried out in a limited number of other countries, a PubMed search covering the period from January 2003 to January 2014 did not return any peer-reviewed publications on the topic of pharmacist perceptions of generic medicines in Ireland. In fact, only 10 publications since 2003 were found in PubMed on the topic of pharmacist perceptions of, and attitudes towards, generic
medicines, indicating that this is a relatively underexplored area internationally.3-12

With Ireland on the cusp of a major modification in health care practices, there are many potential hurdles to overcome during the introduction of such changes.13 The attitudes and behaviors of health care professionals towards generic medicines are pivotal to the successful implementation of the new legislation. The objective of this novel study was to assess these perceptions among community pharmacists in Ireland in the time leading up to the enactment of the new legislation and to determine what challenges might arise as a result of these stakeholder opinions.

Methods

Preparation of Study Instrument

The study instrument was developed based on a recently published review of the usage of generic medicines and how policy changes to promote the use of generic medicines may affect health care provision14 and the personal experience of the primary author and study designer (who has over 15 years of quality management and regulatory affairs within the pharmaceutical and biopharmaceutical industry).

Questions for the semistructured interview were prepared and validated by cognitive testing, the purpose of which was to ensure that the test questions were understood as intended. The purpose of the interviews was to elucidate perceptions relating to general opinion and understanding of generic medicines; behaviors towards generic medicines (e.g., dispensing behaviors in the case of community pharmacists); opinions as to the historical poor usage of generics in Ireland; beliefs held as to the quality and efficacy of generics and how these compare with proprietary (that is, brand-name) medicines; and knowledge and opinion of the impending legislative change.

Cognitive testing was performed with 3 individuals who were first asked the questions to be included in the survey, allowed to provide responses, and after responding were asked what their understanding of the questions were. Amendments were made to questions based on responses from all 3 test participants. The responses of these participants to the interview questions were not included in those finally analysed for this study. The interviews used in the study began after cognitive testing had been completed, and the interview questions had been amended.

Sampling, Recruitment, and Interviews

A convenience sample of community pharmacists was recruited, and interviews completed and analysed. Pharmacists were approached in person, while in the pharmacy, and invited to participate in the study. A verbal explanation of the study was provided, and an invitation letter was offered. One-to-three interviews were carried out with consenting pharmacists between June and October 2012; 34 face to face and 10 via telephone. Interview lengths were as follows: minimum 10 minutes 44 seconds; maximum 36 minutes and 15 seconds; mean 19 minutes 29 seconds. Interviews that were recorded (with the interviewee’s consent) were semistructured and based on the described study instrument (see Table 1). Additional supporting assessment of opinions was completed using a series of structured questions to which participants could select from predefined answers (Table 2). In this instance, a 5-point Likert scale was used with a single response allowed for each question.15 Participants were free to volunteer additional commentary on each question. Furthermore, participants were offered the opportunity to express freely any additional opinions or views at the end of the interview session. Participating pharmacists were located in counties Limerick, Tipperary, Kilkenny, Cork, and Waterford.

<table>
<thead>
<tr>
<th>TABLE 1</th>
<th>Study Instrument: Questions That Formed the Basis for Semistructured Interviews</th>
</tr>
</thead>
<tbody>
<tr>
<td>What is your understanding of what a generic medicine is?</td>
<td></td>
</tr>
<tr>
<td>What is your understanding of how a generic medicine differs from an originator medicine?</td>
<td></td>
</tr>
<tr>
<td>What is your understanding of bioequivalence?</td>
<td></td>
</tr>
<tr>
<td>To the best of your knowledge, what percentage of difference is allowed in terms of bioequivalence between an originator medicine and an equivalent generic product?</td>
<td></td>
</tr>
<tr>
<td>What is your understanding of why generic medicines are cheaper than originator medicines?</td>
<td></td>
</tr>
<tr>
<td>What do you believe about how generic medicines compare with brand-name medicines?</td>
<td></td>
</tr>
<tr>
<td>What is your opinion as to why use of generic drugs in Ireland has historically been much lower than other European countries?</td>
<td></td>
</tr>
<tr>
<td>Have you ever had a patient report that a generic medicine, which you dispensed for them, did not work as effectively as an originator medicine?</td>
<td></td>
</tr>
<tr>
<td>If yes, what type of medicine(s) have you seen this with?</td>
<td></td>
</tr>
<tr>
<td>Can you please give some brief details of what the patient reported having experienced?</td>
<td></td>
</tr>
<tr>
<td>What action did you take in this case?</td>
<td></td>
</tr>
<tr>
<td>Did you then dispense the originator medicine?</td>
<td></td>
</tr>
<tr>
<td>If yes, was there any reported lack of efficacy from the substituted originator medicine?</td>
<td></td>
</tr>
<tr>
<td>Have you ever had a patient report that an originator medicine, which you dispensed for them, did not work as effectively as a generic medicine?</td>
<td></td>
</tr>
<tr>
<td>If yes, what type of medicine(s) have you seen this with?</td>
<td></td>
</tr>
<tr>
<td>Can you please give some brief details of what the patient reported having experienced?</td>
<td></td>
</tr>
<tr>
<td>What action did you take in this case?</td>
<td></td>
</tr>
<tr>
<td>Are you aware of the government’s plans to introduce reference pricing and generic substitution in Ireland?</td>
<td></td>
</tr>
<tr>
<td>What is your opinion of this proposed change in Irish legislation?</td>
<td></td>
</tr>
</tbody>
</table>
Perceptions and Attitudes of Community Pharmacists Towards Generic Medicines

**TABLE 2** Study Instrument: Supporting Structured Questions and Pharmacist Responses

<table>
<thead>
<tr>
<th>Do you strongly agree, agree, neither agree nor disagree, disagree, strongly disagree with the following statements:</th>
<th>Pharmacists, N = 44</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SA/A^a</td>
</tr>
<tr>
<td>Generic medicines are generally of the same quality as originator medicines.</td>
<td>43</td>
</tr>
<tr>
<td>Generic medicines are generally poorer quality than originator medicines.</td>
<td>1</td>
</tr>
<tr>
<td>Generic medicines are generally better quality than originator medicines.</td>
<td>1</td>
</tr>
<tr>
<td>Generic medicines work as effectively as originator medicines.</td>
<td>42</td>
</tr>
<tr>
<td>Generic medicines work better than originator medicines.</td>
<td>0</td>
</tr>
<tr>
<td>Generic medicines don’t work as well as originator medicines.</td>
<td>1</td>
</tr>
<tr>
<td>Generic medicines may be dangerous compared with originator medicines.</td>
<td>2</td>
</tr>
<tr>
<td>Generic medicines are as safe as originator medicines.</td>
<td>44</td>
</tr>
<tr>
<td>Generic medicines are manufactured to the same quality as originator medicines.</td>
<td>35</td>
</tr>
<tr>
<td>Generic medicines are manufactured to a poorer quality than originator medicines.</td>
<td>4</td>
</tr>
<tr>
<td>Generic medicines are manufactured to a higher quality than originator medicines.</td>
<td>0</td>
</tr>
<tr>
<td>Generic medicines are cheaper to buy than originator medicines.</td>
<td>41</td>
</tr>
<tr>
<td>Generic medicines are cheaper because they are of inferior quality to originator medicines.</td>
<td>1</td>
</tr>
<tr>
<td>If I were ill, I would be happy to take a generic medicine if my doctor prescribed it for me.</td>
<td>41</td>
</tr>
<tr>
<td>If I were ill, I would prefer to take an originator medicine rather than a generic medicine, even if it is more expensive.</td>
<td>3</td>
</tr>
</tbody>
</table>

^aStrongly agree/agree. ^bStrongly disagree/disagree. ^cNeutral/no opinion.

Approval of the design and the implementation of this study was granted by the Research Ethics Committee of the Irish College of General Practitioners.

Analysis of Data

Using a grounded theory approach, interviews were transcribed verbatim and imported into NVivo, version 9 (QSR International, Melbourne, Australia) for analysis. Using an inductive process, transcripts were open coded for themes relating to interviewee opinions, perceptions, and behaviors, including any other emerging themes, and the results were analysed using Nvivo. To facilitate visualization and understanding of the numbers of participants holding the perceptions/behaviors that were coded into specific themes, responses were expressed as a percentage of the total number of participants. Interviews were conducted until saturation of data was observed. Analysis was completed by the primary researcher (SD) and reviewed to ensure reliability and rigor of the analysis by a senior investigator (CD).

The coding framework included (but was not limited to) such themes as opinions regarding safety and efficacy; previous experience with use of generics; personal preferences; beliefs regarding historical usage of generics in Ireland; experiences with patient reports regarding generics; prescribing rationales; personal knowledge of, and attitudes towards, generic medicines; and opinions regarding the proposed legislative changes.

Ongoing analysis of themes emerging from the interviews was carried out as interviews were completed. When 4 to 5 consecutive interviews did not lead to the emergence of any new themes, it was determined that data saturation had been achieved and interviewing was concluded.

Results

Supporting quotations from pharmacists are included in Table 3, as referenced in the text.

Analyzing Pharmacist Interviews

Forty-four community pharmacists were interviewed. Demographics of the group are available in Table 4. Participating pharmacists were located in counties Limerick, Tipperary, Cork, and Waterford.

Opinions Regarding Quality, Efficacy, and Safety of Generics

Table 2 shows the analysis of opinions regarding quality, efficacy, and safety of generics. The majority of pharmacists (98%) were of the belief that generic medicines are of the same quality as the originator, with 96% holding the view that they are as efficacious as brand-name products. All of the pharmacists interviewed believed that generics are as safe as the originator. A small number (9%), however, were of the opinion that generics are not manufactured to the same quality as originator medicines and were of the view that generic manufacturing is of a poorer standard. The majority of pharmacists (93%) stated that they would take a generic medicine themselves, with a small number (7%) stating that they would prefer to take the originator rather than an equivalent generic, if offered a choice (reference quotations 1-3, Table 3).
Perceptions and Attitudes of Community Pharmacists Towards Generic Medicines

### TABLE 3

<table>
<thead>
<tr>
<th>Quotation Number</th>
<th>Quotation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>To be honest . . . for any decisions that I make, or anything I say to customers, if it was me or any of my family and I was given the option of a generic medicine I would go for it, I would absolutely take it. Female, aged 30-39 years</td>
</tr>
<tr>
<td>2</td>
<td>I believe that they are equivalent in therapeutic value, and I would have no hesitation in recommending a generic product over a branded one to a customer. Male, aged 19-29 years</td>
</tr>
<tr>
<td>3</td>
<td>I think generic medications are brilliant. To be honest with you, the only downside is people’s perceptions—they think that the brands are better when in reality generics are just as good. Male, aged 18-29 years</td>
</tr>
<tr>
<td>4</td>
<td>On paper they should be the same and should act in the same way, but we have had cases where people have come in and said that they didn’t find a generic as effective as the original and they prefer the original . . . and from customers’ queries, some of them don’t find that they’re the same. Female, aged 30-39 years</td>
</tr>
<tr>
<td>5</td>
<td>[Generic medicines] work the same therapeutically, but I suppose people just have this notion that if it’s cheaper it can’t be as good—that’s the patients perception of it I think. Female, aged 30-39 years</td>
</tr>
<tr>
<td>6</td>
<td>I think, to be honest, any time [a patient has] had a problem with a generic instead of a brand is because they feel that they’re being cheated; they basically feel that they’re getting second best because it’s cheaper. Female, aged 30-39 years</td>
</tr>
<tr>
<td>7</td>
<td>I think if [the patient] started on a generic, and it’s what they know, they prefer that, so I think that it’s maybe the change—it’s a change management issue more than anything else. Male, aged 40-49 years</td>
</tr>
<tr>
<td>8</td>
<td>One woman I can’t convince that the generic coated aspirin would not have caused her to bleed, it’s totally in her mind; you can’t win those battles. Male, aged 50-64 years</td>
</tr>
<tr>
<td>9</td>
<td>If you know what a patient is satisfied with, you generally won’t rock their boat. Female, aged over 65 years</td>
</tr>
<tr>
<td>10</td>
<td>The first thing I would do is I’d try and explain the situation but . . . at the end of the day, I think quite often with people who are coming in, they’ve made up their mind and there’s really very little you can do at that stage. Male, aged 30-39 years</td>
</tr>
<tr>
<td>11</td>
<td>You try to explain to them that it is exactly the same medication and explain to them that it’s the same amount of drug, just called something else, that 500 milligrams of the generic drug is exactly the same, that it’s made in the same way, but then if they’re still going “no, no, no,” we’d give them the original. Female, aged 30-39 years</td>
</tr>
<tr>
<td>12</td>
<td>There have been an increasing number of incidences where people have come back and said that the quality of the solid dosage form is significantly poorer, and there is one company who are particularly culpable in this regard, whereby their tablets crumble on punching from a blister pack. Their capsules are virtually impossible to get out of the blister pack. Now that’s not to say that there’s anything wrong with the actual raw ingredient, with the medication within the solid dosage form, but there are significant shortcomings in the way those solid dosage forms are compounded. And I think that if it’s not rectified, it is going to compromise patients’ attitudes towards generic medicines. Male, aged 30-39 years</td>
</tr>
<tr>
<td>13</td>
<td>I’ve had a couple of issues with a few [generic] tablets—they have disintegrated, over time, and that problem didn’t arise with the original drug . . . but 99% of the time there’s no issue with the quality of [generics]. Female, aged 30-39 years</td>
</tr>
<tr>
<td>14</td>
<td>Packaging-wise, you definitely notice a difference with some of the generics, that you wouldn’t have half as much detail on the packaging, the boxes are quite plain. I know some customers will only take [the original] tablets that actually have the label Monday, Tuesday, Wednesday at the back of them, and a lot of generics won’t have any of that detail on the [foil]. Female, aged 30-39 years</td>
</tr>
<tr>
<td>15</td>
<td>I’d like the generic companies to package their stuff better; if it’s packaged shabbily it gives a bad impression. Now I know it’s nothing to do with the effectivity of the substance, but some of them are very poorly packaged. Male, aged over 65 years</td>
</tr>
<tr>
<td>16</td>
<td>My grandmother in law . . . was on a generic simvastatin which was changed to another simvastatin which happened to be the same color and shape, with no markings, as her blood pressure tablet, and she ended up taking double blood pressure tablets for about 2 weeks. Male, aged 30-39 years</td>
</tr>
<tr>
<td>17</td>
<td>If the demographic of patients you deal with are elderly people, and you know they just don’t like change, they want to stay the same, so you’re kind of on the back foot immediately if you’re trying a new drug. Male, aged 30-39 years</td>
</tr>
<tr>
<td>18</td>
<td>Quotation from a non-Irish pharmacist: My experience with the Irish psyche is that they’re very brand oriented. I don’t know why, but they tend to be very brand oriented. And, I think that could be impacting on why they don’t like generics, they like the original brand . . . but as soon as you tell them it’s a copy, it’s a generic, they will think it’s a second-class drug. Female, aged 40-49 years</td>
</tr>
<tr>
<td>19</td>
<td>I just think people are very used to getting brands; they think all brands are better. It can be to do with the prescribers; some doctors prescribe a brand because that’s what they’ve always known. Male, aged 18-29 years</td>
</tr>
<tr>
<td>20</td>
<td>I think that private patients, paying themselves, don’t mind, but that the people that don’t have to pay are the ones that want to stick to the original brand . . . It’s GMS [General Medical Services] patients that have a problem with it, not the private patients. Female, aged 30-39 years</td>
</tr>
<tr>
<td>21</td>
<td>I think an awful lot of people have it in their head that the generic isn’t as good. As well, medical card patients have commented a few times, ‘It’s because I’m on a medical card that you’re giving me the cheaper tablet.’ That’s the kind of presumption I think that’s out there—people think that because it’s cheaper, they don’t see generic as equivalent, but as a lesser tablet. Female, aged 30-39 years</td>
</tr>
<tr>
<td>22</td>
<td>Get rid of branded generics . . . either it’s a generic or its not, there’s no need for the middle ground of a branded generic. Female, aged 30-39 years</td>
</tr>
</tbody>
</table>
Pharmacist Experiences with Patient Complaints Regarding Generic Medicines

Of the 44 pharmacists, 39 (89%) reported receiving patient complaints associated with use of a generic medicine. Of the 5 pharmacists who did not experience these complaints, 1 pharmacist did not dispense generics. Pharmacists reported that when patients had issues with generics, the main experiences described were that the generics were not as effective or that the patients experienced altered or increased side effects. Twenty-eight pharmacists (64%) expressed an opinion that at least some of the negative experiences reported by patients were not actual, but rather were caused by a nocebo effect (i.e., patients’ preconceived ideas as to a perceived substandard nature of generics led to them having negative experiences with generics) rather than an actual issue with the medication (reference quotations 4-6, Table 3).

Medication types most reported as being problematic included protein pump inhibitors (27%, 12/44), statins (18%, 8/44), inhalers (7%, 3/44), antihypertensives (7%, 3/44), antibiotics (7%, 3/44), antidepressants (5%, 2/44), and analgesics (2%, 1/44).

Conversely, 11 pharmacists (25%) stated that a patient had reported an issue with an originator medicine compared with a generic. In most cases, since the patient had received the generic before the originator medication, pharmacists indicated that, in their opinion, the patient’s preference is often for the medicine first encountered and that such issues are more likely to be due to a change having occurred, rather than an actual issue with the medicine (reference quotation 7, Table 3).

In the situation where pharmacists received complaints from patients related to use of generic medicine and the patients requested the originator instead, 34 pharmacists (77%) stated that they would accede to the patients’ preferences (reference quotations 8-9, Table 3). Only 9 pharmacists (21%) stated that they would attempt to educate the patient (reference quotations 10-11, Table 3).

When asked about the differences between an originator and an equivalent generic, 2 pharmacists (5%) felt that there was no difference. Given that the only requirement for similarity (in terms of ingredients) between an originator product and a generic equivalent is that the same active ingredient be used (excipients may vary) and that generic products are often aesthetically different from the originator, patients can be confused if the differences in appearance and excipient content are not adequately explained to them.

Opinions Regarding Low Historic Usage of Generics

When asked why usage of generics in Ireland has been low in the past, the main reasons given by pharmacists were as follows:

- Lack of generic prescribing (31%, 27/44). The primary reasons given for this opinion were familiarity with trade names on the part of prescribers and their lack of knowledge of the generic names of medicines.
• Lack of government incentive or pressure for generics usage (50%, 22/44).
• The influence of the pharmaceutical industry (i.e., proprietary manufacturers) in Ireland (41%, 18/44).
• Poor understanding of generics by consumers (41%, 18/44).
• Brand consciousness or loyalty on the part of the consumer, including being used to a particular brand and having poor cost consciousness (39%, 17/44).
• The nonallowance of generic substitution (32%, 14/44).

Pharmacist Perceptions of Quality and Patient Issues with Generic Medicines

Three pharmacists (7%) reported having experienced quality issues with generic medicines. Issues reported included crumbling tablets and having difficulty getting tablets out of blister packs. The pharmacists reported that, in their opinion, these issues affect consumer confidence in generic products (reference quotations 12-13, Table 3). Poorer packaging was also mentioned by 4 pharmacists (9%) as being perceived as a negative, and 1 pharmacist (2.3%) stated, anecdotally, that differences between originator and generic packaging can even cause issues for patients (e.g., where an originator brand tablet had the days of the week printed on the foil, serving as a reminder to the patient as to whether that day’s medication had been taken or not, but similar printing was not available with the generics). This led to patient preference for the originator medicine (reference quotations 14-15, Table 3). Nineteen pharmacists (43.2%) also reported the opinion that patients are sometimes resistant to change and that the different aesthetic presentation of generics can cause confusion and medication errors for some patients, particularly the elderly (reference quotations 20-21, Table 3).

Consequently, patient education was seen as a necessary step for wider acceptance of generics, and 15 pharmacists (34%) stated that, in their opinion, patients see generics as being a substandard, or lesser, alternative because they are cheaper, which is described as “own-brand syndrome.” Indeed, 16 pharmacists (36%) expressed the opinion that Irish patients hold a significant preference for branded medications (reference quotations 18-19, Table 3).

Five pharmacists (11.4%) reported having patients who asked for cheaper generics. This was a minority of cases and tended to be limited to private patients, who, according to the pharmacists, have a better understanding and education regarding generics. Pharmacists additionally made reference to General Medical Services (GMS) patients getting more branded medication than private (i.e., self-paying) patients (reference quotations 20-21, Table 3). In Ireland, the GMS, or medical card, scheme is a means-tested scheme available to persons who are unable, without undue financial hardship, to arrange general practitioner, medical, or surgical services. Having a medical card entitles holders and their dependents to a number of free services, including prescription medicines (a dispensing charge applies to prescription medicines). In quarter 4 of 2013 approximately 40% of the Irish population were holders of medical cards. Furthermore, some pharmacists felt that branding of generics should be disallowed because it is contrary to the intent of having generic medication and made it necessary for them to stock multiple “brands” of the same generic medication (reference quotation 22, Table 3).

Opinions Regarding New Legislation

All of the pharmacists interviewed were aware of the Irish government’s plan to introduce reference pricing and generic substitution in Ireland. When asked about their opinions about the new legislation, 35 pharmacists (80%) indicated that they felt positive about the legislation or were accepting of it. Twenty-four pharmacists (55%) were of the opinion that it made financial sense and was necessary for the country, although 20 pharmacists (46%) expressed concerns and reported that they anticipated issues with its practical implementation (reference quotations 23-24, Table 3).

Discussion

According to a PubMed search in January 2014, Irish pharmacists’ perceptions of generic medicines have not been studied in the past. Internationally, a limited number of assessments have taken place for such countries as New Zealand, Portugal, South Africa, Malaysia, France, and Sweden that included studies on views held regarding specific medication types, such as antiepileptic drugs and inhalers. Given the major changes currently underway in the Irish health care system (i.e., the introduction for the first time of reference pricing and generic substitution), the opinions and behaviors of this critical stakeholder group have the potential to be pivotal to the success or failure of the changes being implemented.

In contrast to other reports of reticent pharmacist views, this study has shown that Irish pharmacists were generally positive towards, and accepting of, generic medicines, with many holding the view that they are as effective as the originator, with the exception of nonsubstitutable situations—such as with Narrow Therapeutic Index drugs— and that differences in presentation can be a source of problems for some patients. Very few pharmacists expressed reticent opinions, but 1 of the primary concerns, as has been reported elsewhere, was that confusion caused by differing aesthetic presentations of generic medicines has the potential to be problematic for patients.
While a majority of pharmacists were in favor of the new legislation (with references made to the United Kingdom situation: that no clinical issues linked to a much greater use of generic medicines are seen, thus, the same situation could reasonably be expected in Ireland without risk to patients) about half of the pharmacists interviewed (46%, 20/44) expressed concerns as to the practical implementation of associated changes. Concerns included the impact on the running of the pharmacy as well as on patients. Pharmacists felt that they could meet considerable resistance from patients and that they, being at the “coal face,” may need to spend substantial periods of time explaining the new system to patients, if adequate educative interventions are not put in place by either the government or other interested bodies (e.g., the Pharmaceutical Society of Ireland). Indeed, the requirement for education of the general public to improve opinions and, therefore, increase Society of Ireland). Additionally, generics manufacturers/licence holders may play a role in improving the opinions of consumers regarding their products. One aspect could be to ensure that packaging is of a standard at least equivalent to that of the originator and, where relevant, to ensure that it provides the same facilities for prompting/reminding of patients to take the medication (e.g., the anecdote where a pharmacist stated that continued use of a proprietary brand was due to patient preference for the packaging, as the days of the week were printed on the blister pack foil). An argument can be made for regulators approving generic medicines to require that if patient aids are part of the originator packaging, any generic equivalents must provide similar aids in order to obtain a marketing authorization. Moreover, a theme emerged on the topic of branded generics: while generic substitution makes the issue of pharmacists needing stocks of multiple branded generics moot, (that is, unless a “do not substitute” prescription has been written), pharmacists expressed views that branding of generics should not be permitted as, practical aspects aside, branding of generic medications is not in keeping with the intention of provision of generic medicines. Indeed, a recent report from the Irish Economic and Social Research Institute on the costing of generics in Ireland has shown them to be similar to the original branded medication, thereby not resulting in substantial benefit to either the Irish exchequer or consumer. 

Since improved consumer confidence in generics was considered to be one of the major hurdles to be overcome in improving use of generics in Ireland (similarly noted in other studies4,6), the question was posed by pharmacists: How can this information/education be provided in a manner that is easy for patients to access and understand? While 1 pharmacist showed a patient both the originator and generic products side by side to prove their equivalency (in the case of asthma inhalers), the practicality of doing this on a day-to-day, patient-to-patient basis is obviously something that busy pharmacists cannot undertake. Provision of educational supports could be facilitated, for example, by use of a novel tool, recently published by our group, based on optimized quality of information and reading ability, for development of websites providing health care information.10 The resulting availability of easy-to-read handouts/pamphlets, websites, or similar sources of information may not only provide consumers with the information to dispel myths about generics and, hence, improve their confidence but may also have the dual effect of making the role of the pharmacist easier during a time of upheaval and change.

Patient preference was seen to have a considerable influence on dispensing practices, with many pharmacists (77%, 34/44) acceding to patients’ wishes for brand-name medications, despite the fact that pharmacists believed the majority of issues/complaints from patients regarding generics are not actual, but rather due to the nocebo effect, that is, patients’ prejudices regarding generic medicines (reference quotation 25, Table 3). Pharmacists were of the opinion that this negative patient perception may be based on the fact that generics are less expensive so, therefore, cannot be as good (reference quotation 26, Table 3). Also, pharmacists believed that many negative patient experiences were due to changes in medication and that the first medication that the patient is exposed to will tend to be the preferred option. Therefore, when this is changed, the patient is more likely to experience a problem (reference quotation 27, Table 3).
Perceptions and Attitudes of Community Pharmacists Towards Generic Medicines

Limitations
A possible limitation of this study could be in the selection of community pharmacists, whose opinions may differ from pharmacists working in hospitals or other settings. Furthermore, differing interview settings (some participants were interviewed face-to-face, and others were interviewed over the telephone) might have influenced the data gathered in this study. However, review and comparison of the themes emerging from participants interviewed in different settings did not show any substantial difference in the opinions, perceptions, and behaviors expressed between participants. Moreover, while the authors acknowledge that quantification of qualitative data is sometimes contentious, we chose to adopt this approach in order to best provide easy visualization of results and offer a more comprehensive insight into the patient perspective. The strengths of such an approach have been discussed by Schonfelder in 2011.

A strength of this study is the number of subjects used for qualitative interview; the number of participants in this study compared favorably with the only other semistructured interview-based study that could be found in PubMed (i.e., 16 participants were interviewed for an analogous study in Sweden and 6 pharmacists (from a total of 15 health care professionals) were interviewed for a similar study in South Africa).

Conclusions
Community pharmacists in Ireland hold positive opinions about usage of generic medicines, yet they have concerns about the practical implementation of reference pricing and generic substitution. Concerns were also raised about the impact on patient acceptance due to the varying appearance of generic medicines and regarding the lack of confidence that they observed in the general public in relation to usage of generic medicines.

DISCLOSURES
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S. Dunne was responsible for study design, data collection, and data interpretation and was primarily responsible for the writing of the manuscript, with assistance from C. Dunne. All authors contributed equally to manuscript revision.

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REFERENCES

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Perceptions and Attitudes of Community Pharmacists Towards Generic Medicines

Patient Perceptions of Generic Medicines: A Mixed-Methods Study

Suzanne Dunne  Bill Shannon  Colum Dunne Walter Cullen

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A Method for the Design and Development of Medical or Health Care Information Websites to optimize Search Engine ResultsPage Rankings on Google

Suzanne Dunne, BSc (Hons), MSc; Niamh Maria Cummins, BSc, MSc, PhD; Ailish Hannigan,, BSc, PhD; Bill Shannon, FRCGP, MICGP, MD; Colum Dunne1, BSc (Hons), MBA, PhD; Walter Cullen1,, MB, MICGP, MD

http://dx.doi.org/10.2196/jmir.2632
Generic medicines: an evaluation of the accuracy and accessibility of information available on the internet

Suzanne S Dunne1*, Niamh M Cummins1, Ailish Hannigan1,2, Bill Shannon1, Colum Dunne1,2 and Walter Cullen1,2

Abstract

Background: Internationally, generic medicines are increasingly seen as a key strategy to reduce healthcare expenditure, therefore awareness and knowledge transfer regarding generic medicines are valid areas of research. Although the Internet is a frequently used source of medical information, the accuracy of material found online is variable. The aim of this study was to evaluate information provided on the Internet regarding generic medicines in terms of quality of information and readability.

Methods: Internet searches for information regarding generic medicine were completed, with a pre-defined search term, using the Google search engine, in five English-speaking geographical regions (US, UK, Ireland, Canada and Australia). Search results likely to be looked at by a searcher were collated and assessed for the quality of generic medicine-related information in the websites, using a novel customised Website Quality Assessment (WQA) tool; and for readability, using existing methods. The reproducibility of the tools between two independent reviewers was evaluated and correlations between WQA score, readability statistics and Google search engine results page ranking were assessed.

Results: Wikipedia was the highest-ranking search result in 100% of searches performed. Considerable variability of search results returned between different geographical regions was observed, including that websites identified in the Australian search generated the highest number of country specific websites; searches performed using computers with Irish, British, American and Canadian IP addresses appear to be more similar to each other than the google.com search performed in Australia; and the Canadian google.ca results show a notable difference from any of the other searches. Of the 24 websites assessed, none scored a perfect WQA score. Notably, strong correlation was seen between WQA and readability scores and ranking on google.com search results.

Conclusions: This novel evaluation of websites providing information on generic medicines showed that, of the websites likely to be seen by a searcher, none demonstrated a combination of scoring highly on quality of information (as evinced by WQA score) and readability. Therefore, there is a gap in online knowledge provision on this topic which, if filled by a website designed using the WQA tool developed in this study, has an improved likelihood of ranking highly in google.com search results.

Keywords: Generic medicine, Internet, Medical information, Patient education, Google, Readability

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Background
The Internet has become a source of medical information for patients and healthcare professionals alike. However, the accuracy of information found online may not always necessarily be relied on, and concerns have been raised about the quality of information that may be found, by patients, on the Internet [1-3]. With healthcare costs soaring, many governments are increasingly making use of generic medicines to constrain expenditure. Additionally, many commonly used proprietary medicines have recently, or will in the near future, hit the so-called “patent cliff” – thus enabling generic competition [4-6]. As a result, patients are increasingly likely to be prescribed generic medicines, possibly in place of more familiar proprietary brands. When a patient has medical or healthcare queries, such as questions about generic medicines, the Internet is likely to be one of the first places they will seek information [7]. Therefore, the question should be asked: Is information available on the Internet regarding generic medicines accurate, accessible and of good quality? (For the purposes of this study, the term “accessibility” is used in the context of how readable and understandable the information provided is to the lay reader).

Studies have assessed the use, quality and/or availability of medical/healthcare information available on the Internet in areas as diverse as: inflammatory bowel disease [8], orthodontistry, [9,10] pain, [11] cancer, [12-14] and mental health, [15,16] amongst many others. Such studies often limit themselves to assessing available information in particular countries [17-20]. As many misconceptions exist about generic medicines, and given that healthcare professionals have expressed poor opinions of generics in the past, [21] there is a challenge in ensuring that accurate and relevant information is communicated to the general public. This challenge includes not only the necessity to provide accurate information, to dispel myths and to counter misinformation, but also to present material in a manner that is accessible to the intended audience. It has been reported that, in the case of patients particularly, myths and questions remain about generic medicines, and that accurate information can be difficult to source [22].

The aim of this study was to evaluate the availability of information on the Internet regarding generic medicines. This study additionally assessed whether the information in websites likely to be looked at by patients is accurate (as measured by use of a website quality assessment (WQA) tool) and accessible (as determined by readability and understandability statistics). While much information exists on research into the provision of medical information on the Internet, to the authors’ knowledge, no evaluation has been published specifically regarding quality and accessibility of information on generic medicines. This study aimed to bridge that knowledge gap while evaluating availability and accessibility of that information in several English-speaking countries.

Methods
Choice of search engine
StatCounter, a web analytics company, reported in their “GlobalStats graph” that - for the 12 month period from Jan 2012 to Jan 2013 - Google was the most commonly used search engine globally, holding approximately 90% of the worldwide search engine market [23]. Therefore, as Google is the search engine of choice globally, Google was the search engine used for this study.

Choice of search term
A patient wishing to make an Internet enquiry about a generic medicine is likely to use either the term “generic drug”, or “generic medicine” as their search term. To accommodate both of these, the search term used for this study was “generic medicine OR drug” (without the quotation marks, and with the “OR” capitalised).

The reasoning for this is that Google’s default behaviour is to consider all the words in a search. In order to allow either of the words “drug” or “medicine” to be searched for, the “OR” operator can be used (the OR must be in CAPS). With this search, Google will return SERP (search engine results page) hits that contain the word “generic” and either of the words “drug” or “medicine”. Without the “OR” operator, Google would only return pages that have both the words “drug” and “medicine” on the page, as the “AND” operator is the default [24].

All searches were performed during March and April of 2012.

Inclusion of web sites
A study from 2008 showed that 68% of search engine users click a search result within the first page of results (the default for Google is 10 results per page), and are unlikely to go to the second page of results [25,26]. Therefore, following a search using the defined search term, the results on the first SERP returned that met the following inclusion criteria were assessed: (i) web site written in English; (ii) web site not being a portal providing links to third party sites; (iii) web site not a news story (e.g., as found by Google news search); (iv) web site not a sales website and (v) website not spurious and being related to the topic of generic medicines.

Determination of global variability
To assess global variability, searches were performed in regional Google search engines, google.ie (Ireland), google.co.uk (United Kingdom), google.ca (Canada), and
To assess if Internet Protocol (IP) addresses have any impact on the results obtained, searches were also performed using google.com, on computers in the following five regions: Ireland, United States, Great Britain, Australia, and Canada.

IP stands for “Internet Protocol”. Every device (e.g., computer, tablet, printer etc.) on a computer network has a unique, numeric identifier called an IP address. Similarly to how someone sending a letter would write the intended address on the envelope, a computer’s IP address is used to identify and locate that specific device on a computer network, or on the Internet [27].

Overall, two searches (that is: on the local and .com sites) were performed on computers with an IP address in each of the five regions above, meaning that a total of nine searches were completed.

Assessment of quality of information
The questions in Table 1 – Website Quality Assessment (WQA) Questions for Website Information were asked in relation to each website. The WQA tool was developed for this study as, to the authors’ knowledge, no previous assessment of websites providing information about generic medicines had been published. The WQA tool consists of 22 yes/no type questions, with a point awarded for positive or correct information. No points are awarded where information was lacking, or for inaccurate information. Questions that could not be answered were designated “not applicable” (N/A) and no score awarded. An overall WQA score for each website was totalled from the scores given to each assessment question. (In some cases, just the initial page linked to in the Google search was assessed, however, in the cases where clear and relevant links to other pages containing information of interest within the same website were obvious to the searcher, these were also assessed).

The WQA questions were designed to account for all of the information that a patient might need in order to accurately answer any questions they may have about generic drugs, for example: an explanation as to what a generic drug is and how it differs from a proprietary drug – including price, appearance etc.; explanation of bioequivalence; examples of generic drugs and their proprietary counterparts; information regarding when generic substitution may not be appropriate – e.g., in the case of narrow therapeutic index drugs and any pros or cons of generic medicines.

Assessment of website accessibility
A minimum of a 100-word sample of continuous text from each of the websites was extracted and pasted into Microsoft Word. This text was then analysed using the Flesch Reading Ease score [28] in the MS Word application.

MS Word’s Flesch Reading Ease score is based on a formula developed in 1948 by Rudolf Flesch and determines readability [28]. It is computed using the average number of syllables per word and words per sentence. Syllables-per-word is a measure of word difficulty. Words-per-sentence is an indicator of syntactic complexity.

The Flesch Reading Ease scale ranges from zero to 100. Zero to 50 is very difficult to difficult reading. Eighty and above is easy to very easy reading. Flesch set the minimum score for plain English at 60 [28]. Microsoft’s documentation encourages authors of standard documents to aim for a score of 60 to 70 [29,30].

Additionally, the Flesch-Kincaid Grade Level was used to determine the understandability of each website. The Flesch-Kincaid Grade Level, which was developed in 1975, measures the readability of a document based on the minimum education level required for a reader to understand it [31]. Microsoft recommends aiming for a Flesch-Kincaid score of 7.0 to 8.0 for most documents. According to a 1993 study, the average adult in the U.S. reads at the seventh- grade level and the authors of that study recommended that materials for the public be written at a fifth- or sixth-grade reading level [29].

Statistical analyses
Two reviewers rated each selected website independently and their scores were compared to assess reproducibility of the WQA tool and the readability assessments. Using Statistical Packages for the Social Sciences (version 20.0), the intra-class correlation coefficient (ICC) was used to measure reproducibility. Spearman’s correlation coefficient (r_s) was used to measure the association between the ranking of websites with WQA scores and readability assessments. Absolute values of r_s > 0.3 were considered to represent moderate correlations, > 0.5 were considered strong correlations. The scores from the developer of the assessment tool (SD) were used in the correlation analyses. The correlation between ranking of websites and WQA scores was also used to demonstrate the predictive validity of this newly developed assessment tool.

Results
Determination of websites for assessment
Thirty-eight (38) unique hits (i.e. individual search results) were identified from the first SERPs of the nine searches performed. Of these, 15 hits were discarded for the reasons described in the methodology or were amalgamated with another hit. (For example, the website entitled: EGA - Basics of generic medicines was a hit on both of the IE searches. Additionally, the main EGA website was a hit on the google.co.uk search. As both
relate to the same website, the results were combined into one and the EGA website assessed as a single site, rather than individual pages).

An additional website – entitled Generics Are The Same - was added during the rating exercise as it was directly referred to in the *Canadian Generic Pharmaceutical Association* website and is also published by the Canadian Generic Pharmaceutical Association. As the Generics Are The Same website is the explanatory arm of the *Canadian Generic Pharmaceutical Association* website it was decided to also assess this website as a patient accessing the first website is very likely to follow links through to the second. This was the only example of an associated website being assessed.

Overall, a total of 24 individual websites were assessed using the WQA tool. Results of the assessments for each of the 24 websites are displayed in Table 2, which additionally shows the ranking on the Google search results page for each website assessed, in each of the individual domain searches.

**Analysis of websites from search results**

Visual analysis of the search results (Table 2), including comparison of the international searches, showed that

### Table 1 Website quality assessment (WQA) questions for assessing generic medicine website information (Continued)

<table>
<thead>
<tr>
<th>Question</th>
<th>Answer and score</th>
<th>WQA score awarded</th>
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<tbody>
<tr>
<td>Is there accurate information given on how generic bioequivalence, or generic manufacturing may affect NTI drugs?</td>
<td>Yes = 1</td>
<td>No = 0</td>
</tr>
<tr>
<td>Is any inaccurate information given regarding NTI drugs?</td>
<td>Yes = 0</td>
<td>No = 1</td>
</tr>
<tr>
<td>Are &quot;pros&quot; of generics mentioned?</td>
<td>Yes = 1</td>
<td>No = 0</td>
</tr>
<tr>
<td>Are any &quot;cons&quot; of generics mentioned?</td>
<td>Yes = 1</td>
<td>No = 0</td>
</tr>
<tr>
<td>Is the difference between proprietary and non-proprietary names accurate?</td>
<td>Yes = 1</td>
<td>No = 0</td>
</tr>
<tr>
<td>Generic prescribing mentioned and explained accurately?</td>
<td>Yes = 1</td>
<td>No = 0</td>
</tr>
</tbody>
</table>

| Is there accurate information given on how generic bioequivalence, or generic manufacturing may affect NTI drugs? | Yes = 1 | No = 0 |
| Is any inaccurate information given regarding NTI drugs?                 | Yes = 0 | No = 1 |
| Are "pros" of generics mentioned?                                        | Yes = 1 | No = 0 |
| Are any "cons" of generics mentioned?                                     | Yes = 1 | No = 0 |
| Is the difference between proprietary and non-proprietary names accurate? | Yes = 1 | No = 0 |
| Generic prescribing mentioned and explained accurately?                  | Yes = 1 | No = 0 |

<table>
<thead>
<tr>
<th>Total score</th>
<th>Flesch reading ease score</th>
<th>Flesch Kinkaid grade level</th>
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Dunne et al. BMC Medical Informatics and Decision Making 2013, 13:115
http://www.biomedcentral.com/1472-6947/13/115

Page 4 of 13
Wikipedia (a collaboratively edited, multilingual, free Internet encyclopedia supported by the non-profit Wikimedia Foundation) was the number one ranked search result in all searches completed. This is consistent with findings in other studies [32,33] including a study reporting that Wikipedia is the 6th most accessed website on the Internet globally [34] and, therefore, likely to be visited by those seeking medical information.

After Wikipedia, the following five websites were the most likely to be used by searchers, based on the search terms used in this study:

- About.com’s page entitled *Generic Drugs: Know the Benefits and Differences of Generic Drugs*
- MedicineNet.com’s page: *Generic Drugs, Are They as Good as Brand Names?*

### Table 2 Websites assessed with their rankings on the different google searches and website quality assessment (WQA) score

<table>
<thead>
<tr>
<th>Website title</th>
<th>Google SERP ranking*</th>
<th>WQA score</th>
<th>Flesch reading ease score</th>
<th>Flesch Kinkaid grade level</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Generic drug - Wikipedia, the free encyclopedia</td>
<td>1 1 1 1 1 1 1 1</td>
<td>16</td>
<td>49.1</td>
<td>10.2</td>
</tr>
<tr>
<td>2 Generic Drugs: Know the Benefits and Differences of Generic Drugs – about.com</td>
<td>2 2 2 3 2 2 10 6</td>
<td>16</td>
<td>53.5</td>
<td>8</td>
</tr>
<tr>
<td>3 Generic drugs, Are They as Good as Brand Names? - MedicineNet.com</td>
<td>3 3 3 5 5 3 3 2</td>
<td>11</td>
<td>42.5</td>
<td>11.3</td>
</tr>
<tr>
<td>4 Understanding Generic Drugs</td>
<td>4 5 4 6 3 4 6 7</td>
<td>16</td>
<td>57.2</td>
<td>9</td>
</tr>
<tr>
<td>5 Branded and generic medicines</td>
<td>5 7 6 2 6 9</td>
<td>17</td>
<td>36.7</td>
<td>14.6</td>
</tr>
<tr>
<td>6 WHO</td>
<td>Generic Drugs</td>
<td>6 4 5 7 5 5 5 5</td>
<td>10</td>
<td>32.9</td>
</tr>
<tr>
<td>7 RxList – Facts About Generic Drugs</td>
<td>7 6 4 8</td>
<td>9</td>
<td>79.3</td>
<td>4.6</td>
</tr>
<tr>
<td>8 EGA - European Generic medicines Association</td>
<td>8 9 8</td>
<td>13</td>
<td>22.9</td>
<td>12</td>
</tr>
<tr>
<td>9 National Medicines Information Centre - Generic Prescribing</td>
<td>8</td>
<td>17</td>
<td>31</td>
<td>11.5</td>
</tr>
<tr>
<td>10 Generic Drugs - What are Generic Drugs?</td>
<td>10</td>
<td>15</td>
<td>25</td>
<td>17.1</td>
</tr>
<tr>
<td>11 GPhA - Generic Pharmaceutical Association</td>
<td>9 7 9</td>
<td>14</td>
<td>39.4</td>
<td>14.5</td>
</tr>
<tr>
<td>12 Generic / Brand Drug Name Table</td>
<td>10 10 3</td>
<td>10</td>
<td>48.6</td>
<td>10</td>
</tr>
<tr>
<td>13 Generic vs Brand Name Medicines</td>
<td>4</td>
<td>9</td>
<td>60</td>
<td>8</td>
</tr>
<tr>
<td>14 AIDS, Drug Prices and Generic Drugs</td>
<td>9 10</td>
<td>11</td>
<td>27</td>
<td>15</td>
</tr>
<tr>
<td>15 Canadian Generic Pharmaceutical Association</td>
<td>2</td>
<td>12</td>
<td>55.6</td>
<td>9.3</td>
</tr>
<tr>
<td>16 Generics Are The Same (2)</td>
<td>(2)</td>
<td>12</td>
<td>43.7</td>
<td>12.5</td>
</tr>
<tr>
<td>17 Generic Drugs In Canada: A Policy Paper</td>
<td>4</td>
<td>8</td>
<td>37.3</td>
<td>14</td>
</tr>
<tr>
<td>18 Benefiting from Generic Drug Competition in Canada: The Way Forward</td>
<td>7</td>
<td>11</td>
<td>54.4</td>
<td>7.7</td>
</tr>
<tr>
<td>19 Generic Drugs – The Same Medicine for Less Money</td>
<td>7</td>
<td>10</td>
<td>75.1</td>
<td>5.6</td>
</tr>
<tr>
<td>20 Generic Drugs</td>
<td>9</td>
<td>6</td>
<td>42</td>
<td>11.9</td>
</tr>
<tr>
<td>21 The Generic Medicines industry Association of Australia</td>
<td>3</td>
<td>13</td>
<td>24.4</td>
<td>12</td>
</tr>
<tr>
<td>22 Australian Prescriber: Frequently asked questions about generic medicines</td>
<td>4</td>
<td>15</td>
<td>22.2</td>
<td>12</td>
</tr>
<tr>
<td>23 Pricing of PBS Medicine - Medicare Australia</td>
<td>8</td>
<td>4</td>
<td>34.3</td>
<td>12</td>
</tr>
<tr>
<td>24 Questions and answers on generic medicines</td>
<td>10</td>
<td>10</td>
<td>32.9</td>
<td>12</td>
</tr>
</tbody>
</table>

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*Abbreviations used: IE Ireland, UK United Kingdom, US United States, CA Canada, AU Australia.

This website “Generics Are The Same” was not a result in the original searches, but was directly linked to the Canadian Generic Pharmaceutical Association website, which was the second result returned in the google.ca search. As it is likely that a patient finding the first website would link into the second, it was added to this study and WQA assessed with the other websites found.
• The US Food and Drug Administration (FDA)’s page entitled Understanding Generic Drugs
• NetDoctor.co.uk’s page entitled Branded and generic medicines
• The World Health Organisation’s page: Generic Drugs

These six websites (Wikipedia and the five others above that appear most often) all appear in at least six of the nine searches completed (Table 2).

SERPs returned to searchers during this study demonstrate that a search, using identical search terms and performed in the local Google search engine, compared to that performed on the same computer (i.e., same IP address) but in the google.com domain, can provide substantially different results (Table 2). Other notable observations from Table 2 include that the European Generic Medicines Association (EGA) website was a hit in three of the four searches conducted in Europe (it was not a result in the google.com UK search) but was not seen in any of the other searches. This could indicate a possible regional variance. However, the FDA website (an American website) was a hit in all searches, with the exception of the Canadian google.ca search (it was a hit in the Canadian google.com search). Additionally, it was noted that the results of the Australian searches had the highest level of country/domain specific websites with six unique hits observed between the Australian google.com and google.com.au searches that were not seen elsewhere.

The google.com searches performed using computers with Irish, British, American and Canadian IP addresses appear to be more similar to each other than the google.com search performed in Australia. The Australian google.com profile is noticeably different from the other search results with two unique websites not present in the other google.com searches.

Interestingly, the Canadian google.ca results show a distinct difference from any of the other searches due to the absence of most of the websites seen in other regional searches, with the exception of Wikipedia and Canadian websites.

WQA scores
The WQA tool (Table 1) employed 22 yes/no type questions to assess the quality of information contained in each website. From a maximum available score of 22, the highest score awarded was 17 - awarded to two websites: (i) Netdoctor.co.uk – Branded and generic medicines and (ii) The Irish National Information Centre’s publication - Generic Prescribing (websites numbered 5 and 9 respectively in Table 3). However, only the Netdoctor.co.uk site was also in the top six sites indicated by the Google search rankings. The Irish National Information Centre’s publication was a result only in the google.ie (Irish IP address) search, and its likelihood of being seen outside Ireland considered small.

WQA scores of 16 (the second highest WQA score awarded) were given to three websites: (i) Wikipedia’s Generic drug page, the highest ranking website by Google search result, (ii) About.com’s page entitled Generic Drugs: Know the Benefits and Differences of Generic Drugs and (iii) the FDA’s Understanding Generic Drugs (websites numbered 1, 2, and 4 respectively in Table 3). All three websites were situated in the top six websites most observed in the Google SERPs obtained.

The remaining two sites seen in the top six most highly returned websites scored WQA scores of 11 (MedicineNet page, website number 3 in Table 3) and 10 (WHO page, website number 6 in Table 3), indicating that the extent and quality of information in these websites is less than the other four top results, and considerably lower than some of the other websites assessed in this study. This indicates that some websites likely to be seen by searchers contain the relatively poorer or less accurate information on generic medicines.

The association between WQA score and Google search ranking was investigated and a moderate to strong correlation (defined as an absolute value of Spearman’s correlation coefficient > 0.3) was found for searches done in the google.com domain (Figure 1 and Table 4). The most commonly identified websites, i.e., ranked 1, 2 etc., tended to have higher WQA scores. No such correlation was found in the local searches (i.e., google.ie/.co.uk/.ca and .com.au).

Accessibility scores
A Flesch Reading Ease score of 60 or greater and a Flesch Kinkaid Grade Level of less than 8 are recommended for general ease of reading.

Three of the websites assessed had a Reading Ease score of greater than or equal to 60: (i) RxList – Facts about Generic Drugs, (ii) Generic Drugs – The same Medicine for Less Money and (iii) Generic vs Brand Name Medicines (numbered 7, 19, and 13 respectively, in Table 3).

Five of the assessed websites had Grade Level scores of 8 or less: (i) RxList – Facts About Generic Drugs, (ii) Generic Drugs – The Same Medicine for Less Money, (iii) Benefiting from Generic Drug Competition in Canada: The Way Forward, (iv) Generic vs Brand Name Medicines, and (v) Generic Drugs: Know the Benefits and Differences of Generic Drugs – about.com (numbered 7, 19, 18, 13, and 2 respectively, in Table 3).

Therefore, as the three websites with the best Reading Ease scores (numbered 7, 19 and 13, respectively, in Table 3) also have appropriate Grade Level scores, it can be determined that those three websites would be the easiest for a member of the public, without a scientific background, to read and understand. However, as those
three websites scored relatively low with respect to quality of information they contained - with WQA scores of 9, 10, and 9 respectively (Figure 2) – our study could not assess a site with good readability statistics and containing high quality information. However, analogously to what was demonstrated for WQA scores, Reading Ease scores also demonstrated a relationship with ranking on Google searches. Results from this study indicated that easier to read websites rank higher in Google.com search rankings (Figure 1 and Table 4). Finding statistically significant correlations was limited by the small sample sizes (at most 10 websites in each domain) but a statistically significant correlation was found for the US google.com search ($r_s = -0.64$, Table 3).
Figure 1 Scatterplots of WQA score, Reading Ease score and Grade level against website ranking on US google.com search.
Table 4 Correlation between WQA, reading ease score and grade level with ranking using Spearman’s correlation coefficient ($r_s$)

<table>
<thead>
<tr>
<th>Google domain</th>
<th>n</th>
<th>WQA</th>
<th>p-value</th>
<th>Spearman’s $r_s$</th>
<th>Flesch reading ease score</th>
<th>p-value</th>
<th>Spearman’s $r_s$</th>
<th>Flesch Kinkaid grade level</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IE / .com</td>
<td>8</td>
<td>-0.49</td>
<td>0.220</td>
<td>-0.33</td>
<td>0.24</td>
<td>0.570</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IE / .ie</td>
<td>10</td>
<td>0.06</td>
<td>0.866</td>
<td>-0.64$^*$</td>
<td>0.048$^*$</td>
<td>0.58</td>
<td>0.082</td>
<td></td>
<td></td>
</tr>
<tr>
<td>UK / .com</td>
<td>8</td>
<td>-0.38</td>
<td>0.352</td>
<td>-0.48</td>
<td>0.233</td>
<td>0.43</td>
<td>0.289</td>
<td></td>
<td></td>
</tr>
<tr>
<td>UK / .co.uk</td>
<td>9</td>
<td>-0.51</td>
<td>0.160</td>
<td>-0.58</td>
<td>0.112</td>
<td>0.44</td>
<td>0.232</td>
<td></td>
<td></td>
</tr>
<tr>
<td>US / .com</td>
<td>7</td>
<td>-0.67</td>
<td>0.097</td>
<td>-0.64</td>
<td>0.119</td>
<td>0.68</td>
<td>0.094</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CA / .com</td>
<td>8</td>
<td>-0.38</td>
<td>0.352</td>
<td>-0.48</td>
<td>0.233</td>
<td>0.43</td>
<td>0.289</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CA / .ca</td>
<td>5</td>
<td>-0.70</td>
<td>0.188</td>
<td>0.10</td>
<td>0.873</td>
<td>-0.30</td>
<td>0.624</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AU / .com</td>
<td>8</td>
<td>-0.34</td>
<td>0.404</td>
<td>0.29</td>
<td>0.493</td>
<td>-0.38</td>
<td>0.352</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AU / .com.au</td>
<td>10</td>
<td>-0.10</td>
<td>0.787</td>
<td>0.00</td>
<td>1.000</td>
<td>0.33</td>
<td>0.359</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*p-statistically significant at 5% level of significance.

p = 0.048). The top ranked sites in all domains also had lower Flesch Kinkaid GradeLevel scores (Figure 1 and Table 4).

Reproducibility
Comparing scores of two independent reviewers (SD and NC) show that, for WQA assessments, almost perfect agreement was seen on average (ICC = 0.94). Similar analysis of readability of the websites using Flesch Reading Ease score and Flesch-Kinkaid Grade Level showed moderate to strong levels of agreement between the two reviewers (ICC value = 0.71 and 0.63, respectively).

Readability scores were assessed by taking a section of text from the website and calculating readability statistics using MS Word. As each rating was independent, different sections of text were likely to be selected from each of the websites assessed. This variation is likely to account for the lower levels of agreement for the reading assessments, compared to the WQA tool. Given the subjectivity of this type of readability assessment, it is reasonable that a moderate consistency was observed throughout the websites assessed.

Overall, the WQA and readability scores demonstrate acceptable reproducibility between two reviewers.

Discussion
This novel study is the first to assess the websites most likely to be read by a patient searching the Internet for information about generic medicines. More specifically, using the WQA tool developed here, we determined that those websites were all lacking at least some of the information that the authors considered appropriate and relevant for inclusion. However, notably, none of the websites appeared to contain purposefully inaccurate information (as determined by the WQA tool); rather they lacked information that was considered important and that would have gained the website a higher score in our assessments.

Use of Wikipedia as a primary source of information is prevalent and increasing worldwide, [33,34] despite known shortcomings and criticisms, [2,35], including bias and the potential for the information it contains to be corrupted. With use of Wikipedia by clinicians as well as medical students increasing, [35] (and ease of access and ease of understanding being the main reasons cited for its usage amongst medical students), [36] it is reasonable to expect that patients also access this resource when searching for medical information. Very pertinent to this, is the fact that Wikipedia is available in both English and Simple English – where the Simple version is intended to be more accessible by use of simplified language and limited vocabulary. Indeed, guidelines provided by Wikipedia on writing of Simple information may be useful to those interested in distributing medical information to the general public [37,38].

Recognition of Wikipedia’s prevalence has sparked debate as to whether clinicians should engage in editing Wikipedia to help provide accurate information to patients [39,40]. As the results of this study indicate that patients searching for information on generic medicines in each of the subject countries are likely to find Wikipedia as the first result (Table 2), there appears to be an onus on governments or government-provided healthcare systems to engage with Wikipedia in order to ensure that the information contained therein is impartial as well as accurate. Indeed, given the prevalence of internet –derived information and social networking associated with “web 2.0”, [41] this is an area likely to increase in importance in the future.

Of the other five websites which were most likely to be accessed by a searcher (see Table 2), about.com is a resource website containing articles and other information organized into “channels” on various topics. Freelance writers, referred to as “Guides”, author the articles.
About.com differs from Wikipedia in that it does not allow editing by anyone, and it makes use of advertising. The about.com website pages assessed in this study were written by a "patient empowerment guide" without, according to the website, a scientific or medical background. In addition, this website contained frequent, prominent advertising placed in close proximity to the article information, making it possible for searchers to confuse actual information provided with advertising content. The MedicineNet website contained similar levels of
advertising to those seen in about.com. However, the author and editor of this page held MD and PhD degrees, respectively, which may endow more credibility. Nonetheless, this website was ranked in the lowest two of the six websites most likely to be seen by searchers, with a WQA score of 11 (see Table 2). The FDA's page Understanding Generic Drugs is a resource likely to be trusted by patients as it is written by the US pharmaceutical regulator. The lack of advertisements also lends the website a more professional, and possibly trustworthy, appearance than some of the other websites assessed during this study. The netdoctor.co.uk information on generic medicines, awarded the highest WQA score calculated, was written by a pharmacist. This, as with MedicineNet, may add weight to the website's content in a searcher's opinion. While there are a small number of adverts on this site, they are not as close to the information or as obvious as in other websites discussed above. Finally, the WHO website, while being a reputable source which is likely to be recognised, trusted and possibly even sought out by searchers, unfortunately contains relatively little information useful to the general public when seeking information on generic medicines. Indeed, this was the lowest WQA scoring website of the six most likely to be viewed by searchers. Moreover, it scored low for readability, again reducing the likelihood of it being used by the general public. Interestingly, 7 of the 15 websites that were discarded (i.e., not assessed by WQA) were sales websites. This suggests strongly that a searcher looking for information about generics may encounter a high number of websites selling generic medicines, representing a potential patient safety/public health risk given current concerns with counterfeit medicines being sold online [42]. Only one other website received the highest awarded WQA score (of 17) – a bulletin published by the National Medicines Information Centre at St. James's hospital in Dublin, Ireland. While the information in this article was of high quality, its readability scores were relatively low. This is probably because the intended audience for this bulletin was healthcare professionals and, thus, the language used in the article would have been appropriate for them. However, while the bulletin provided high quality information, it would have been of little use to a non-scientist. In summary, for websites providing medical information to the general public, quality of information must be allied to language and syntax that matches the reading and comprehension abilities of the intended audience.

In the UK, about 16% of adults are described as “functionally literate”, meaning that they have the literacy levels at or below those expected of an 11-year old [43]. In the Republic of Ireland, the International Adult Literacy Survey revealed that one in four adults have problems with even the simplest of literacy tasks [44], with similar rates being seen in the US [45] and Canada [46]. A key finding of this study was that there is a correlation between good readability statistics and higher ranking on google.com searches (Table 4), indicating that more readable websites are more likely to be found by searchers. However, as the top scoring websites investigated during this study for Reading Ease scored relatively poorly for WQA, we were not able to investigate a website with both good information and good readability. Importantly, the implication is that a searcher looking for information on generic medicines is unlikely to identify a website that is both readable and contains high quality information (as evidenced by a high WQA score). Therefore, there appears to be a gap in knowledge provision that could be filled by a website with high quality information, explaining to the general public specifically what generic medicines are (including dispelling any myths about generic drugs) which is also designed and written to maximize readability. Given the correlations between WQA score and readability statistics and ranking on google.com SERPs evinced by this study, it could reasonably be suggested that (general popularity of sites such as Wikipedia and the FDA site excepted) such a website would return an enhanced score on a google.com search (across varying IP regions). However, the finding of statistically significant correlations in this study was limited by the small sample sizes, as the study was designed to mimic how a typical searcher would use results of a Google search (i.e., not going beyond the first page of results) [47]. An interesting question arising from this is: who is responsible for provision of such a website? Is it the responsibly of the State to provide good quality, readable medical information to its citizens? Or should it fall to private stakeholders to provide such a service?

Conclusions

Recommendations from a 2010 report on the proposed model for introduction of generic substitution and reference pricing in Ireland stated that communication of information about generic medicines to the general public would be key for the success of the proposed change in the Irish healthcare system [48]. Whatever the answer, many patients using the Internet for medical information do not differentiate between high- and low-credibility sources of information when perceiving the quality of the information provided [49] and, therefore, it is clear that medical information websites need to be assessed for quality of information and readability by the intended audience before they are published on the Internet. The WQA tool developed during this evaluation of generic medicine-related site proved effective and relatively easy-to-use in that context, and may, if adapted, be suitable for assessment of other types of medical/healthcare information websites [50].
Abbreviations

Competing interests
All authors declare that they have no competing interests.

Authors’ contributions
SD conceived of the idea for the research, designed and conducted the analysis, gathered and interpreted the data and drafted, revised and finalised the manuscript. NC aided in data gathering and interpretation and provided critical review of the manuscript. AH completed statistical analysis of the data, provided critical review of the manuscript and final approval of the version to be published. CD provided critical review of the manuscript and final approval of the version to be published. WC provided critical review of the manuscript and final approval of the version to be published. All authors read and approved the final manuscript.

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What answers does the Internet provide for patients in Ireland with questions about generic medicines?

Suzanne S Dunne, Niamh M Cummins, Ailish Hannigan, Bill Shannon, Walter Cullen and Colum P Dunne

http://dx.doi.org/10.1177/1741134314542542
Appendix 3

Additional papers published, in parallel with this thesis, while registered for this degree.
An evidence-based assessment of primary care needs in an economically deprived Urban community

C. Power  R. O’Connor  S. Dunne P. Finucane W. Cullen  C. Dunne

http://dx.doi.org/10.1007/s11845-013-0913-2
Journal of Medical Ethics
2013, 40, pp. 710-713

The first survey of attitudes of medical students in Ireland towards termination of pregnancy

James M Fitzgerald, Katherine E Krause, Darya Yermak, Suzanne Dunne, Ailish Hannigan, Walter Cullen, David Meagher, Deirdre McGrath, Paul Finucane,

Calvin Coffey, Colum Dunne

http://dx.doi.org/10.1136/medethics-2013-101608