Author's response to reviews

Title: 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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Author's response to reviews: see over
15 November 2012.

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Dear Dr. D’Souza

Following your communication of 31st October, the revisions to the manuscript are now complete.

The authors would like to thank the reviewers for their additional comments and suggested changes, which we feel have improved the manuscript appreciably. Each of the points made by reviewers 2 and 3 have been addressed, and our detailed responses have been appended to this letter. The additional editorial requests have also been addressed.

To facilitate further review, sections where major changes have been made on this revision are highlighted in green in the revised manuscript. Previous changes, which were made following the first review, are indicated in yellow highlight. However, if there are any clarifications required, or if there are any additional queries, please do not hesitate to contact me.

We trust that the revised manuscript is now acceptable for publication and look forward to hearing from you in due course.

Regards,

Suzanne Dunne.
**RESPONSES TO REVIEWERS**

The authors thank the reviewers for their comments and suggested changes. Each of these points has now been addressed, and our responses are detailed below. We believe that in complying with the suggested changes, and in taking into consideration the points raised by the reviewers, the manuscript has been improved considerably.

**Detailed author responses:**

| Atholl Johnston | Therapeutic agents where generic substitution is not supported by medical opinion not discussed. | The authors had complied with the reviewer’s previous comments by expanding that section of the manuscript to include additional information. In response to the reviewer’s suggestion, the manuscript has now been further amended to include the following text, with appropriate references (Page 26). This deals specifically, with the challenge of where medicines should be prescribed by brand to ensure continued efficacy and safety of treatment.

“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 [90]. Similarly, the British National Formulary (BNF) currently recommends brand prescribing... |
| --- | --- | --- |
for a number of medicines and drug classes, namely modified release diltiazem [91 p132]) and ciclosporin [91 p583], while in July 2008 the Northern Ireland Health and Social Care Board issued an extensive list of medicines considered unsuitable for generic prescribing [92] which included narrow therapeutic index drugs, modified release preparations, controlled drugs including patches, inhalers, and multi-ingredient products.

| A further discussion of where the “cost savings” go would be useful. | This was not something that the authors had considered. It makes a useful addition on Page 32 where we have added:

“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 [109] 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 [110] 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 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.”

<table>
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<tr>
<th>Brian Godman</th>
<th>i) Page 4, line 30</th>
<th>The following text has been inserted (now page 4). “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.”</th>
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<td>ii) Page 5, lines 4 - 7</td>
<td>The text referred to by the reviewer has now been removed. INN prescribing and benefits arising that include avoidance of patient confusion and non-optimal use of pharmacist time is now discussed more fully on Page 30. “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 pharmacist visit, resulting in pharmacist (and, presumably, physician) being invested in explaining to the patient that their new drug is the</td>
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same as the previous one [105]. 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.”

iii) Page 6, Reference 5

This reference was included in the text (page 6, line 9, end of sentence).
(Now on page 5, line 9, same position).

iv) Pages 6-10

The following text has been inserted.
Page 7:
“... However, it should be noted that variations between batches of originator drugs may themselves threaten patient safety. In a study published 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 changed manufacturing processes.”
Page 10:
“... 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].”

v) Page 7

The work of Kesselheim et al has now been included in balancing this section (now page 6-7).
“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].”

vi) Page 10, line 26

This section has now been amended.
Page 11:
” 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
| vii) Summary of pharmaceutical regulations, and history of drug development | The intent of this article 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. To fulfill this objective the authors feel that the summary of pharmaceutical regulations, along with the associated figure, is an integral part of the text; similarly the section on drug development. The aim is to show clearly how regulation and manufacture of generics differs from that of originator medicines, and where generic medicines fit into the drug life cycle model. |
| viii) Pages 19-21 | Meta-analyses before single case histories: this section has now been modified considerably (now page 22).

Circumstances for avoidance of generic substitution: this section has now been modified considerably. The following has been inserted (page 26):

“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 [90]. Similarly, the British National Formulary (BNF) currently recommends brand prescribing for a number of medicines and drug classes, namely modified release diltiazem [91 p132]) and ciclosporin [91 p583], while in July 2008 the Northern Ireland Health and Social Care Board issued an extensive list of medicines considered unsuitable for generic prescribing [92] which included narrow therapeutic index drugs, modified release preparations,
controlled drugs including patches, inhalers, and multi-ingredient products.”

Treatments of epilepsy remain controversial: This sentence has now been modified (now page 23).

Ref 68: This sentence has now been tempered and is more reflective of the Ferner et al position.

Ref 69: This has now been dealt with.

ix) Page 20 The text cited does not contain anecdotal reports/comments, but rather refers to two peer-reviewed publications, as referenced.
The authors are of the belief that this information has a place in a balanced review article about the origins, history and current usage of generic medicines. This section has been rewritten to ensure there is no misapprehension regarding the literature cited and additional examples have been include to reinforce the point being made in this section.

x) Page 22 This is an insightful contribution. The following text has been inserted: (page 28) “As a result of this poor use of 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 considerable savings that are possible without compromising patient safety or efficacy of treatment.”

xi) Page 24, line 29 This has now been amended as suggested by the reviewer. The terms “generic” and “INN” are now used as appropriate and not interchangeably.

xii) Page 25, lines 1-2 This has now been amended as suggested by the reviewer.

xiii) Page 26, line 27 This has now been amended as suggested by the reviewer, with the insertion of the following text (now page
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<td>33): “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 [113] and may, actually, represent an aversion to erosion of profits rather than accurately reflect the market.”</td>
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<td>xiv) Page 27, line 13</td>
<td>This has now been amended as suggested by the reviewer. The following text has been inserted (now page 34): “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 originator medicines may also differ depending on country of origin if sourced via parallel importation).” The text has been amended to read: (page 34) “…and financial incentives that have led to effective implementation of a generic medicine policy by stakeholders recognizing the need to conserve resources [119].”</td>
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<td>Page 27, lines 19</td>
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<td>xv) Reference</td>
<td>Use of these 1997 references was as an indicator of the opinions of healthcare professionals in Ireland as they relate to generic medicines. This was the most recent review of its type that could be sourced by the authors and we believe, the current economic crisis in Ireland notwithstanding, that this information has a part in this review article</td>
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<td>xvi) Page 28, lines 19-21</td>
<td>This has now been removed as suggested by the reviewer.</td>
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<td>xvii) Page 31, lines 17-25</td>
<td>This has now been amended as suggested by the reviewer.</td>
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<td>(xviii)</td>
<td>(Not in reviewer’s comments)</td>
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<td>xix) Page 32</td>
<td>This has now been removed as suggested by the reviewer.</td>
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