Reviewer's report

Title: Generic Medicines: Do You Get What You Pay For? A Review Of The Differences And Similarities Between Generic Drugs And Their Proprietary Counterparts, Including Economic Benefits Associated With Usage Of Generic Medicines, Using Ireland As A Case Study.

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Reviewer: Brian Godman

Reviewer's report:

1. Question posed by the authors new and well defined?

The only part of article that is relatively new is the discussion/ data regarding the proposed changes in Ireland.

Unfortunately, the authors seem unaware/ have not bothered to include the extensive number of peer reviewed publications over the past few years comparing and contrasting differences between generics and originators and the outcomes, as well as policies among European countries to try and obtain low prices for generics as well as enhance their utilisation versus originators (ATC level 5) or patent protected products in the class/ disease area (ATC Levels 3 and 4).

In addition, the objectives are not clearly stated. In fact the whole paper lacks a formal academic structure of Introduction, Objectives, Methodology, Results/ Findings and Discussion/ Conclusion. This is a pity as there is some good information intermingled with opinions and a plethora of inappropriate web-based references.

Consequently, this is a major revision to the paper before potential acceptance.

2. Are the methods appropriate and well described, and are sufficient data provided to replicate the work?

Unfortunately there is no methods section in this paper – so the answer is no.

In addition, as mentioned a number of references are from web-sites and a weekly newspaper for doctors in Ireland (Irish Medical news) rather than peer-reviewed publications further downgrading the paper as being of an acceptable academic standard.

Again both areas are ‘Major revision’ before acceptance.

3. Are the data sound and well controlled and (4) Does the manuscript adhere to the relevant standards for reporting and data deposition

Again the answer to both is no. This goes back to a lack of an academic structure
to the paper as well as any methodology.

Overall, I believe it is acceptable in an academic peer-reviewed journal for the authors to quote EMA and FDA websites when discussing their regulations. However, a number of other important references from peer-reviewed journals are currently excluded (although freely available/accessible in e.g. Pub Med). In addition, a number of references from websites are incomplete. Alongside this, a number of references/citations are taken from conferences where peer-reviewed publications exist, and there is also heavy reliance on the Irish Medical News which I believe is a weekly newspaper for physicians and not subject to peer review. Finally, there are also a number of inaccuracies in the paper.

In more detail (Major revision unless stated):

A) General

• Better to say originators and generics rather than brand names and generics since there are ‘branded generics’ in a number of European countries – I am not sure of the situation currently in Ireland

• Other European countries have had reference pricing for the molecule (ATC level 5) or the Class (ATC Level 3 and 4) for some time, e.g. work of Steven Simoens such as ‘The impact of reference-pricing systems in Europe: a literature review and case studies. Expert Rev. Pharmacoeconomics Outcomes Res. 2011; Trends in Generic Pricing Exp Review Clin Pharmacol 2008; International comparison of generic medicine prices in CMR and Opinion 2007; and Generic medicine pricing in Europe: current issues and future perspective JME 2008. In addition, Godman, Shrank, Wettermark 2010 in Pharmaceuticals and Puig-Junoy J in Pharmacoeconomics 2010. This will be addressed under specific points below (but needs to be acknowledged)

• The EU Commission has grave concerns with some of the activities of pharma companies delaying/ blocking entry of generics highlighted in their report (http://ec.europa.eu/competition/sectors/pharmaceuticals/inquiry/communication_en.pdf) and editorial by Exeter in the Lancet August 2009 – not mentioned by the authors. This needs to be addressed and included if talking generally about enhancing availability/ utilisation of generics to help countries conserve resources

• Ireland has much more to learn from other countries than the other way around, e.g. Godman, Shrank, Andersen et al in Expert Rev PE and OR 2010 illustrate that the lack of demand-side measures in Ireland led to increased prescribing of patent protected PPIs and statins after the availability of generic omeprazole and simvastatin and away from increased prescribing of multiple sourced PPIs and statins, appreciably enhancing prescribing costs versus countries with multiple and intensive demand side measures such as Sweden and the UK. In addition, the authors provide data at the bottom of page 9/ top of page 10 on just how low prices in the UK can go for generics with the implementation of the ‘M’ and ‘W’ scheme (scheme not mentioned by the authors – References include the OFT Report for the UK as well as e.g. McGinn et al Expert Review PE and OR 2010) – something that can potentially be a goal for Ireland. Consequently, the
discussions on how other EU countries can learn from Ireland need to be appreciably amended

- Persistence with drugs is higher in the US with generics than patented drugs with the Tier co-pay system (work of Will Shrank, e.g. The Implications of Choice Archives Int Med 2006; Patient, Physician, Pharmacy, and Pharmacy Benefit Design Factors Related to Generic Medication Use – Soc Int Med 2007). In addition, can be limited concerns among patients towards generics – although still some education needed among both to enhance the prescribing/utilisation of generics e.g. Ann Pharmacother. 2011 - Physician perceptions about generic drugs and ‘Is There a Relationship Between Patient Beliefs or Communication About Generic Drugs and Medication Utilization?’ Med Care 2009). These points need to be borne in mind when discussing the US.

More specifically:

- Page 4 - I am not sure why the authors quote an obscure Australian reference to discuss the criteria for generic drugs and then go on to discuss criteria in Europe and US. Much better to just concentrate on the FDA and EMA regulations – Discretionary change

- Page 5 – Whilst intuitively the cost of generics should be lower than originators as no R & D costs, the cost of generics can vary up to 36 fold or more across countries depending on the molecule – so not the whole truth (work of Steven Simoens, e.g. CMR reference already quoted) – Discretionary change

- Page 6 – No reference that the tolerance limits of originator products are similar to those for generics

- Page 6 – There are generic products for e.g. phenytoin with caution in some countries with switching (Ferner et al BMJ 2010). However, Shrank, Kesselheim and colleagues in their extensive review of brand name versus originator drugs for CV diseases published in JAMA in 2008 including warfarin, propafenone, etc., could not find superior outcomes with originators vs. generics. This is supported by reference 12 as well as similar tolerance in bioequivalence between batches of originators and generics.

- Page 9 – Mention is made of the price of generics vs. pre-patent loss originator prices. However, as the authors have already shown – there can be very low prices in the UK – also Sweden (Godman, Wettermark et al Exp Rev 2009). So good to include comments about this especially with Northern Ireland as a border to Ireland. In addition, reference is made to the EGA website for this data (without mentioning the URL) – where published data exists, e.g. work of Perry as well as Simoens and colleagues

- Pages 10 to most of page 18 – I am not sure this data is needed and detracts from an article that is essentially about generics. Consequently, I would recommend excluding it (Discretionary change)

- Page 18 Not sure Figure 2 needed and comments above (Discretionary change)

- Page 20 – Not sure most of the historic data needed as dealing with the current situation to enhance prescribing efficiency in Ireland through increased use of
generics at lower prices (Discretionary change)

• Page 21 – I have major concerns with most of the data quoted at the start of this page as anecdotal and reported in a non-peer reviewed source (Irish Medical Times). The two peer reviews by Shrank, Kesselheim and colleagues would dispute this (above and Seizure Outcomes Following the Use of Generic versus Brand-Name Antiepileptic Drugs - A Systematic Review and Meta-Analysis - Drugs 2010; 70 (5): 605-621) – alongside similar tolerance levels for the bioavailability of different batches of originator and generic drugs. Alongside this, even with atypical antipsychotics – no problems with e.g. clozapine after the first formulation in the US (Alessi-Severini S, Honcharik PL et al J Clin Psychiatry 2006 and Paton C Br J Psychiatry 2006, or generic olanzapine - Araszkiewicz AA, Szabert K et al Exp Rev PE and OR 2008.

• Page 21 - I agree there can be concerns with oral bisphosphonates as expressed by Kanis and colleagues in Osteoporos Int. January 2012. Consequently care with monitoring patients (better reference than a non peer-reviewed conference presentation)

• Page 21 - Care in some countries with switching drugs for epilepsy – although a recent meta analysis showed limited/ no differences between the outcomes of generics vs. originators although different for case histories/ observational studies (also seen in Talati et al - Efficacy and safety of innovator versus generic drugs in patients with epilepsy: a systematic review. Pharmacotherapy 2012). As a result, caution in e.g. UK as mentioned by Ferner et al in their BMJ article (above). This also applies to originator products as the manufacturing processes can change leading to problems, e.g. lamotrigine via GSK (Patel et al – Changed constitution without change in brand name--the risk of generics in epilepsy. Epilepsy Res. 2012)


• Page 22 – Need to cite the meta analysis by Kesselheim, Shrank and colleagues in JAMA mentioned above when discussing propafenone as an alternative viewpoint (in a well respected journal)

• Page 23 – Need to disassociate generics vs. originators and generics vs. patent protected products in a class as different strategies.

• Page 23 – No URL for reference 75 or 77. Likely also to be references among the publications of Simoens and Perry documenting rates of generic utilisation in Ireland (needs checking)

• Page 23 – No rationale is given for the fall in the rate of generic prescribing (Ref 80) in Ireland – again is this linked to the encouragement from external stakeholders to prescribe originators/ patent protected products – especially as very different to the UK with its high voluntary INN prescribing rates (mentioned later on)? (discretionary change)
• Page 25 – Reference 83 refers to rates in 2001. Interesting given the fact that many high volume products lost their patents in 2000 onwards including PPIs, statins, ACEIs, etc.

• Page 25 – Ref 80 – who was there and how were these suggestions taken forward? (Discretionary change)

• Page 26 – Also suggest including e.g. McGinn et al mentioned earlier which discusses the training of UK physicians to prescribe by INN name where possible, which is carried on and encouraged in the community (adds further weight). In addition, may be more scientific to discuss INN prescribing rather than ‘generic’ prescribing (discretionary change)

• Page 26 – What has happened since Mid 2010 - as other countries have introduced measures to enhance prescribing efficiency through increased use of generics at a faster rate especially given reference 91 (Discretionary change). One way around this in Ireland would be the instigation of INN prescribing as not sure/ not totally clear from the paper whether generics in Ireland are ‘branded generics’. In any event, INN prescribing rates as seen in the UK once generics are available (up to 98/99% for some – e.g. McGinn et al and Bennie et al Exp Rev PE and OR 2012) will negate the need for the pharmacist to inform patients of the cheaper option (Discretionary change)

• Page 27 – Many peer reviewed references (already discussed) should be used in place of Ref 91 for an academic publication. The same applies to Ref 92. In addition, the authors need to distinguish whether one is dealing with reference pricing for the molecule (ATC Level 5) or the class/disease area (ATC Levels 3 and 4). In either situation, typically patients have to cover the difference themselves for a more expensive drug than the current referenced price molecule. Pharmacists in a number of EU countries can undertake generic substitution with targets in e.g. countries such as France (Sermet et al Pharmacoeconomics 2010) – however, rare when measures pertain to ATC Levels 3 and 4

• Page 27 – One wonders with Ref 93 and 94 how pharmacists are remunerated in Ireland. If based on a % of the cost of the drugs – then not surprising apparent scaremongering about the proposed reforms as do not see shortages North of the Border with their much lower prices for generics. In addition, in countries such as Lithuania even with their small populations again do not see shortages even with low prices for generics (Garuoliene et al Exp Rev PE and OR 2011). The same may apply to the Physicians with potentially reduced marketing activities from the Pharma Companies (one way to explain the very different utilisation patterns seen between e.g. UK and Ireland for PPI and statin prescribing once generics become available in the class discussed earlier). Having said this, recognised situations across countries where substitution should not occur. However, a minority of cases as seen in e.g. Ferner et al in the BMJ discussed earlier (Discretionary change)

• Page 28 – No mention in citing Ref 66 that the degree of bioavailability tolerance is the same between successive batches of originators as generics

• Page 28 – The quote by Professor Bradley is wrong given the references
already quoted and many others since reference pricing (ATC Levels 3 to 5) have been in operation in many European countries for many years – so suggest removing it

• Page 28 – Why Australia when generally talking about EU and USA? Good to mention the many published papers by Karolina Anderssen in Sweden on the impact of compulsory generic substitution in 2002. Also good to mention that confusion with different brand names when ‘branded generics’ (leading to some of the problems discussed) can be alleviated by INN prescribing from the outset (as seen in the vast majority of occasions in the UK) (Discretionary change)

• Page 28 – Good to quote the work of William Shrank when reviewing the US as well as the fact that compliance rates are higher with generics as lower co-pays (above)

• Page 28 – Ref 99 – Such fears can be overcome by stressing the strict criteria for the licensing of generics in EU as well as programmes by e.g. France to allay key stakeholder fears regarding generics and resultant savings (Sermet et al discussed earlier)

• Page 29 – High INN rates in the UK stem from medical education onwards (as mentioned earlier) – this is irrespective of any devolution of budgets as seen in e.g. Scotland (where no devolution down to practices) vs. England (studies mentioned earlier). In addition, in both situations GPs are regularly monitored for the rate of the prescribing of generic vs. patented products in a class such as for PPIs, statins and ACEIs/ARBs under the ‘Better Care Better Value – BCBV schemes (Internet plus references mentioned earlier)

• Page 30 – Care with interpreting the findings of the GP Fundholding Scheme in the UK as generics in many high volume products such as the PPIs, statins, ACEIs, SSRIs, etc., only became available from 2000 onwards. This has been replaced by e.g. BCBV schemes, practice formularies linked with incentives, etc.

• Page 30 – There is acceptance among health authorities/health insurance agencies across Europe that some products should not be substituted, e.g. Ferner et al in BMJ for the UK and in Sweden with the MPA adjudicating regarding possible substitution between different branded generics and the originator (e.g. Wettermark, Godman et al PE 2008 and Godman, Wettermark et al Exp Rev PE and OR 2009)

Comments regarding the conclusion are below (number 5).

5. Are the discussions and conclusion well balanced and adequately supported by the data

Again, unfortunately no to date.

Suggested changes include (mandatory unless stated):

i) Page 31

• First paragraph – Not backed up by published evidence as shown by e.g. high INN prescribing rates in the UK – especially once a product loses its patent
(apart from a minority of patients); similarly in other European countries including France (with their high substitution targets), Sweden (compulsory substitution unless in a minority of situations), Germany – where high acceptance of generics, etc. One of the recognised issues though is that there can be problems with a minority of products – hence accepted situations where substitution is discouraged/ not allowed as outlined in e.g. UK BNF (Ferner et al and publications by Martin Duerden), Sweden (Wettermark, Godman et al 2008 and Godman, Wettermark, et al 2009), Austria (where again generics discouraged if the authorities have concerns with substitution), etc. It is also increasingly recognised that there can be patient confusion with ‘branded generics’, and patients potentially being dispensed a different named drug of the same active ingredient on each occasion. As a result, seeing increasing moves across Europe to introduce INN prescribing (voluntary in the UK, compulsory in e.g. Estonia and Lithuania) and actively being considered in e.g. Austria, Slovenia and Sweden. In the meantime, computer terminals in e.g. Sweden whereby patients can check their prescribing history in the pharmacy (as discussed in Godman, Wettermark et al 2009).

• Second paragraph – again not necessarily true as there have been a considerable number of publications including meta analyses by the group in Harvard comparing outcomes between generics and originators across a wide number of disease areas (previously mentioned above). Comment also about bioequivalence between different batches of originators – same tolerance levels as generics.

• Third paragraph – Some good points. However, these have been considered in a number of European countries with active and successful programmes by payers not only to enhance the use of generics versus originators but also increasingly against patent protected products in the same/ similar classes (references already mentioned). In addition, in the US higher compliance with generics than patented products (work of Will Shrank). This needs to be mentioned.

ii) Page 32

• Important to mention in the first paragraph that Ireland can learn from the plethora of examples across Europe including France, Lithuania, Sweden and the UK.

• Second paragraph – again the authorities in Ireland can learn from authorities in other European countries on ways to successfully enhance the prescribing and dispensing of generics versus originators and patent protected products in a class/ related class, as well as obtain low prices for generics.

• Third paragraph – the various publications endorse that education particularly of physicians and patients is key – so endorse the comments made in this and the last paragraph. This especially given the points made in the fourth/last paragraph about further products losing their patent.
6. Do the title and abstract accurately convey what has been found

No – given the substantial peer-reviewed information that has not been included in the paper

7. Is the writing acceptable?

The style of writing is acceptable as this was an easy to read paper.

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I declare I have no competing interest.