Reviewer’s report

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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Reviewer: Brian Godman

Reviewer’s report:

i) Page 4 line 30 - why is Ireland making these changes, e.g. need to conserve considerable resources given the current economic climate and its likely persistence, etc. This needs to be added in

ii) Page 5 Lines 4 to 7. The authors have missed the point. There can be confusion if patients are dispensed a different branded generic on each occasion leading to the need for pharmacists to spend time discussing with patients that their new drug is the same as the previous one (discussed under Sweden in Godman B, Abuelkhair M, Vitry A, Abdu S et al. Payers endorse generics to enhance prescribing efficiency; impact and future implications, a case history approach. GABI 2012; 1(2): 21-35) else they make ask again for the drug/ just not take it. However, patient confusion regarding names is not an issue if there is INN prescribing from the outset (as witnessed in the UK). Indeed, one of the benefits of INN prescribing is that it reduces patient confusion between names when these change from the originator to the generic, as well as negate any need to pay pharmacists to spend time with patients allaying fears that the products are similar although different names or reward the pharmacists to achieve certain substitution rates as seen in France (also mentioned in the GABI article and ref 27)

iii) Page 6 - Ref 5 has been left out of the text - although included in the references

iv) Pages 6 to 10 generally - the authors talk a great deal about the bioequivalence for generics but not between different batches of originator products - which typically have the same tolerance levels. This is demonstrated by the situation with originator lamotrigine that the authors discussed, with the new manufacturing process making successive batches at the top end of the tolerance limits leading to problems (page 20)

v) Page 7 - The meta analysis by Kesselheim et al (which the authors quote) would suggest similar outcomes whether patients were on generic warfarin or originator warfarin, which undermines some of the comments made in lines 11 to 18. The authors (lines 20 to 26) then go on to make a very good case for generics - which is ignored in other parts of the paper

vi) Page 10 line 26 (as well as lines 8 and 9 page 18) - the main reason why companies of originator products can charge so much is that they can get away
with it. The price requested bears no relation to R & D costs (typically 10 to 15% of total turnover) but everything to do with the perceived value of the product versus the price of current standards on the market. In the case of generics, prices can vary 35 fold between molecules/ countries - so whilst there are no R & D costs to recoup (some of the work of Steven Simoens that has been quoted) - pricing again is down to the local regulations and in a number of cases bears little relation to the cost of goods

vii) I am not sure that a summary of the pharmaceutical regulations including biosimilars in pages 11 to 14, as well as the history of drug development, is that relevant to an article on generics - especially given the relatively limited resources actually spent on R & D versus total turnover by the major pharmaceutical companies. The same also applies to Drug Development (pages 15 to 18). These pages could potentially go into an Appendix if the readers are interested in these comments

viii) Pages 19 - 21 - I would prefer to see the results of the 2 meta analyses in CV drugs and those for epilepsy first before single case histories. In addition, acknowledge that there are some areas (a minority) where substitution should be avoided such as potentially bisphosphonates for the reasons quoted as well as examples in the UK - contained in the BNF, etc . Ferner R, Lenney W, Marriott J. Controversy over generic substitution. BMJ 2010; 341: 1341-3 and ref 73. Also state that treatments for epilepsy remain controversial as demonstrated by the meta analysis of Kesselheim versus the advice in the UK BNF and SIGN in Scotland (Ferner et al and ref 73) before launching into the second paragraph of Page 19 and into 20. Also page 19 at the bottom - Ferner et al (ref 68) only talks about a minority of situations (you would not recognise this from the way the sentence is written). I would agree that generic substitution should not be practised with the existing high INN prescribing rates in the UK in view of these limited areas - and so I would object to it myself. Ref 69 quoted has to also be balanced against the work of Will Shrank and colleagues to show that persistence with generic medicines is appreciably greater than with branded drugs in the US - helped by considerably lower co-payment for generics versus originators (especially now with a number of plans having $4 co-pays/ item for generics vs. for instance up to $30 - $50/ items for certain branded products). The same applies to potential comments after Line 8 page 28

ix) Page 20 - how often are there differences in excipients between originators and generics that could cause problems? If no figures exist/ can be quoted, then I would suggest removing paragraph 2 as again anecdotal reports/ comments

x) Page 22 - fourth paragraph. Ref 25 shows that in Ireland with its limited demand side measures, the prescribing of multiple source PPIs and statins went down following their availability vs. e.g. Sweden and the UK and the prescribing of patented products in the class went up. The reverse was seen in the UK and Sweden leading for instance expenditure/ 1000 inhabitants/ year for the GMS population being approx. 10 times that of Sweden. This puts the low use of generics among the GMS population in Ireland into perspective - hence the considerable need for reforms in Ireland given the financial crisis there and the ability to quickly realise considerable savings without compromising care with
appropriate measures
xi) Page 24 line 29 (and others). INN prescribing does not mean generic prescribing (although called as such in a number of papers). This is because an originator product will be dispensed by the pharmacist if no generic is available, e.g. Nexium and Crestor are still being dispensed as esomeprazole and rosvuastatin respectively in the UK
xii) Page 25 lines 1 to 2 - Bennie et al (in Bennie M, Godman B, Bishop I, Campbell S. Multiple initiatives continue to enhance the prescribing efficiency for the proton pump inhibitors and statins in Scotland. Expert Review Pharmacoeconomics and Outcomes Research 2012; 12: 125-130) also discuss high INN prescribing rates in Scotland
xiii) Page 26 - Line 27 - also need to mention that this happens in Lithuania even with considerably reduced prices of generics versus originators. One wonders if the rhetoric of the pharmacists in Ireland is due to their current remuneration package especially if this is based on a % of the drug purchasing costs
xiv) Page 27 - Line 13 - equally in the UK the shape and colour of originators can vary between batches if these come from different countries via parallel importation. Lines 19 to 25 - may be worth saying that good acceptance of substitution by the physicians in Sweden as they recognised the need to conserve resources
xv) Page 28 Lines 9 to 14 - how relevant are 1997 references - especially given the current economic crisis in Ireland?
xvi) Page 28 lines 19 - 21. Not relevant. The BCBV indicators in the UK refer to the prescribing of generic PPIs, statins and ACEIs vs. patent protected PPIs, statins (and ezetimibe) and ARBs - which the authors go onto describe. Not discussed is the fact that physicians in the UK are rewarded for achieving target lipid and BP levels and do this well with generics at appropriate doses (Quality and Outcome Framework - QOF), e.g. McGinn et al (quoted), Bennie et al (above) and Von#ina L, Strizrep T, Godman B, Bennie M et al. Influence of demand side measures to enhance renin-angiotensin prescribing efficiency in Europe; implications for the future. Expert Rev Pharmacoeconomics and Outcomes Res 2011; 11:471-81
xvii) Page 31 - lines 17 to 25. The meta analyses of Kesselhem quoted earlier, the high INN prescribing rates in the UK, etc., would suggest an alterantive scenario to that currently discussed - so some need for balance in a scientific article. In addition, high INN prescribing is seen as good medical practice in the UK and not leading to problems if exceptions are noted (described above). However, as quoted by the authors and e.g. Bennie et al - there can be considerable financial rewards for high INN prescribing, encouraging the prescribing of generics first line vs. patented products in a class/ related class, etc. This is especially important given the current financial situation in Ireland. Such a situation in the UK also negates the negative comments in the last paragraph of page 31 - especially where there are strict bioequivalence rules governing both generics and successive batches of originators leading to good correlations in bioavailability between the two as discussed earlier by the
authors.

xix) Page 32 - First and second paragraph. Such comments have NO PLACE at all in a scientific and objective article about generics and their potential benefits and so should be cut out