Reviewer's report

Title: What do people really think about generic drugs? A systematic review and critical appraisal of literature on stakeholder perceptions of generic medicines.

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Reviewer: Brian Godman

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Critique Dunne et al – generics by Brian Godman – Division of Clinical Pharmacology, Karolinska Institute, Stockholm, Sweden and Strathclyde Institute of Pharmacy and Biomedical Sciences, Strathclyde University, Glasgow, UK

A) General

I found the paper easy to read. The authors are to be congratulated on a thorough review of the literature encompassing these three important stakeholder groups. The findings can be used by health authorities world-wide to enhance the use of generics where there are continuing concerns.

B) Good points include:

• Questions posed – good and well defined with all 3 stakeholder groups included
• Paper well written (above)
• Appreciable number of references sourced and critiqued
• Study aims good as well as a robust methodology
• Data included was sound – but potential areas for consideration.
• Good number of constructs regarding physicians (page 12), pharmacists (page 16) and patients (pages 19/20), with lower costs for generics being a major consideration among physicians for their prescribing (page 13) – mentioned also for patients (top of page 21)
• Acknowledging there may well be bias in the papers written, e.g. middle of page 18 and middle page 27
• Providing patients with more information about generics had a significantly positive effect of their willingness to take them (half way down page 26 – ref 48) – as well as potential confusion between ‘generic’ and genetic’ – which has not typically been addressed by health authority personnel. In addition, at the bottom of page 26 – showing that mistrust still exists among some patient groups towards generics – which must be overcome to enhance their use. This is especially important for patients with lower socioeconomic status (half way page 27). The same about lower prices does not always translate into lower quality (lines 3 and 4 page 28)

C) Areas to be considered/ addressed

Areas to be considered/ addressed include the introduction and the discussion
where more content could be inserted especially for health authority personnel – which I believe is a key audience that the authors are seeking to target based on their recommendations.

Regarding the introduction - no mention of the fact that e.g. (i) generic medicines can be priced as low as 2% to 10% of pre-patent loss prices leading to considerable savings across countries - as a result multiple strategies have been introduced across countries to enhance their use, (ii) strict regulations for bioequivalence in e.g. USA and Europe – with numerous studies reporting that generic drugs’ AUC and Cmax differed only by 3–4% on average from those of the originator with poorer manufactured products that do not fulfil key criteria for bioequivalence not granted marketing authorisation as generic drugs. As a result, (iii) meta-analysis and other studies have shown no difference in outcomes between originator and generic CV medicines, antibiotics, anti-psychotics and anti-epilepsy medicines (although continuing controversy – see below) as well as high voluntary INN prescribing in some countries (apart from a limited number of well-known examples). Despite these facts there have been repeated attempts by originator manufacturers to cast doubt on the quality of generics – leading to concerns by the EU, etc. There have also been fines for misinformation – e.g. the French government with Sanofi and generic clopidogrel, etc.

However, we are aware of continuing concerns with generics among key stakeholder groups – etc. – hence the paper.

Consequently, might be best to start with for instance (discretionary):

• Increased use of generic medicines is essential to sustain healthcare systems given increasing pressure on resources including requests for funding new premium priced medicines at typically over US100,000/ patient/ year or course of more (Refs in Godman B, Malmstrom RE et al. Are new models needed to optimize the utilization of new medicines to sustain healthcare systems? Expert review of clinical pharmacology. 2015;8(1):77-94). Increased use of low cost generics (providing quality assured) will also help patients in lower and middle income countries where a high proportion of their income is currently spent on medicines – details in e.g. Wagner AK, Graves AJ et al. Access to care and medicines, burden of health care expenditures, and risk protection: results from the World Health Survey. Health policy. 2011;100(2-3):151-8


• A number of studies have been undertaken to document potential savings from the increased use of generics including both developing and developed countries, e.g. (i) Godman, Bishop et al; (ii) Cameron A Laing R. Cost savings of switching private sector consumption from originator brand medicines to generic equivalents. Available at URL:

• Care should not be compromised as generics …. (definition on page 4 as well as Baumgartel C. Myths, questions, facts about generic drugs in the EU. GaBI Journal. 2012;1:34-8) - with numerous studies reporting that generic drugs’ AUC and Cmax differed only by 3–4% on average from those of the originator - with poorer manufactured products that do not fulfil key criteria for bioequivalence not granted marketing authorisation as generic drugs (references in Baumgartel) – seen also recently with e.g. clopidogrel where concerns with some generics Baumgartel C, Godman B et al. What lessons can be learned from the launch of generic clopidogrel? GaBI Journal. 2012;1:58-68. As a result, meta- analysis and other studies have shown no difference in outcomes between originator and generic CV medicines (including warfarin), antibiotics, anti-psychotics and anti-epilepsy medicines, e.g. (i) Kesselheim AS, Misono AS et al. Clinical equivalence of generic and brand-name drugs used in cardiovascular disease: a systematic review and meta-analysis. JAMA: 2008;300:2514-26; (ii) Kesselheim AS, Stedman MR et al. Seizure outcomes following the use of generic versus brand-name antiepileptic drugs: a systematic review and meta-analysis. Drugs. 2010;70:605-21; (iii) Corrao G, Soranna D et al. Similarity between generic and brand-name antihypertensive drugs for primary prevention of cardiovascular disease: evidence from a large population-based study. European journal of clinical investigation. 2014;44:933-9; (iv) Veronin M. Should we have concerns with generic versus brand antimicrobial drugs? A review of issues. JPHSR
This confidence is translated into for instance high voluntary INN prescribing rates in the UK (Godman, Bishop et al) at 98-99% for a number of high volume generics apart from well known situations including lithium, theophyllines, AEDs, modified release preparations and immunosuppressants. In these situations, originator prescribing endorsed – e.g. Ferner RE, Lenney W, Marriott JF. Controversy over generic substitution. BMJ. 2010;340:c2548 and Duerden MG, Hughes DA. Generic and therapeutic substitutions in the UK: are they a good thing? British journal of clinical pharmacology. 2010;70:335-41. The UK Medicines Agency has recently issued a very good review of AEDs – which ones to prescribe by originator and which OK for INN name - https://www.gov.uk/drug-safety-update/antiepileptic-drugs-new-advice-on-switching-between-different-manufacturers-products-for-a-particular-drug (may be worth including this) – similar for e.g. tacrolimus – URL: http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON15575

As a result, concern by the European Commission and others when originator companies question the suitability of generic medicines – In COMMUNICATION FROM THE COMMISSION - Executive Summary of the Pharmaceutical Sector Inquiry Report. Available at URL: http://ec.europa.eu/competition/sectors/pharmaceuticals/inquiry/communication_en.pdf. A recent example is clopidogrel leading to a fine for Sanofi from the French Authorities for their disinformation in - Editorial. Generic bashing: effective but illegal. PRESCRIRE INTERNATIONAL 2013;22(144):307.

Benefits of generics can also include increased adherence - e.g. work of Will Shrank, e.g. Shrank WH, Hoang T et al. The implications of choice: prescribing generic or preferred pharmaceuticals improves medication adherence for chronic conditions. Archives of internal medicine. 2006;166(3):332-7. In addition, a recent review by Barbui and colleagues regarding antidepressants - Barbui C, Conti V. Adherence to generic v. brand antidepressant treatment and the key role of health system factors. Epidemiology and psychiatric sciences. 2014:1-4. No doubt in the US further helped by the US$4 co-pay for generics vs. e.g. $10 – 20/item for preferred patented oral medicines and considerably higher for non-preferred oral medicines/ biologicals - Harshali K. Patel, Michael L. Johnson and Sujit S. Sansgiry. Consumers’ intention to use generic-drug discount programmes JPHSR 2012, 3: 205–212.

Then into concerns and why researching key stakeholder groups in these 3 areas. These include concerns with quality of generics, activities by pharmaceutical companies including inducements, etc., to physicians/pharmacists (good review including Korea in Yu SY, Yang BM, Kim JH. New anti-rebate legislation in South Korea. Applied health economics and health policy. 2013;11:311-8), concerns with confusion if patients dispensed different...

D) Specific issues (minor but essential)

i) General
The order of the references needs improving – typical to start with the lowest number first and work up. Often not in order which is a concern

ii) Specific
• Page 4 near the end - I am not sure about the comment that ‘Many countries worldwide have introduced systems for substitution’. It may be better to say ‘Many countries have introduced substitution as well as other measures to increase the prescribing and dispensing of generic versus originators’. This is because most countries in Europe use an internal reference price system with patients covering the additional cost themselves for a more expensive product than the current referenced price generic (which encourages the patients to request the cheapest generic with reluctance to pay a higher price for e.g. the originator – in e.g. Vogler S. The impact of pharmaceutical pricing and reimbursement policies on generics uptake: implementation of policy options on generics in 29 European countries#an overview. GaBI Journal. 2012;1:93-100 and Simoens S. A review of generic medicine pricing in Europe. GaBI. 2012;1:8-12) with only a few European countries implementing compulsory substitution – e.g. Sweden (Karolina Andersson’s work - Andersson K, Sonesson C et al. What are the obstacles to generic substitution? An assessment of the behaviour of prescribers, patients and pharmacies during the first year of generic substitution in Sweden. PDS. 2005;14:341-8 and Andersson K, Jorgensen T, Carlsten A. Physicians’ opinions and experiences of the Pharmaceutical Benefits Reform. Scandinavian journal of public health. 2006;34:654-9) or compulsory INN prescribing (in Garuoliene K, Godman B, Gulbinovic J et al. European countries with small populations can obtain low prices for drugs: Lithuania as a case history. Expert review of pharmacoeconomics & outcomes research. 2011;11:343-9) or voluntary INN prescribing with no substitution currently in pharmacies – UK in Godman, Bishop et al and Ferner et al. In Germany – reforms in place to encourage patients to request the cheapest generic (may not always be in the best financial interest of pharmacists) – e.g. http://www.gabionline.net/Country-Focus/Germany/Policies-and-Legislation and http://www.gabionline.net/layout/set/print/Country-Focus/Germany/Market-Analysis. In the US – US$4 co-pay for generics and in LMIC countries typically only the generics in public facilities as part of essential medicine lists. However, good to discuss concerns which are then explored in depth.

• Page 13 – Good to compare comments on e.g. warfarin with the review of Kesselheim et al including 5 RCTs looking at warfarin (here or in the discussion). Not surprising comments on AEDs – so one area to be careful regarding substitution (good to acknowledge this in the discussion when discussing
potential future policies that health authorities could implement to enhance the use of generics to save monies).

- Page 16 – Start of new paragraph when mentioning Germany (line 3) – care about stating that German pharmacists cautious as (i) only dry powder inhalers were discussed and (ii) the first author of the paper was with GSK – who have a vested interest to ensure their dry powder inhalers are not substituted!

- Page 27 – Top – these comments refer to extended release preparations only. What about the immediate release preparations – presumably no problem? The UK authorities acknowledge that ER preparations can be a concern (as seen in Ferner et al and Duerden) – so may be good to include some mention that concerns with other ER preparations

- Pages 29/ 30 – Much more could be inserted regarding recommendations. I agree that further research may be needed among pharmacists. However, regarding equivalence – now have the summaries of Baumgartel as well as details of a number of published meta-analysis showing no difference in a number of product classes/ disease areas between generics and originators – acknowledging that there are difficulties in some product classes/ disease areas including AEDs (as mentioned), transplantation, etc. Recommendations to increase the use of generics could also be taken from the recent review by Moe-Byrne and colleagues - Moe-Byrne T, Chambers D et al. Behaviour change interventions to promote prescribing of generic drugs: a rapid evidence synthesis and systematic review. BMJ open. 2014;4:e004623. In addition, France with its multiple campaigns (summarised in e.g. Godman B, Abuelkhair M, Vitry A et al. Payers endorse generics to enhance prescribing efficiency; impact and future implications, a case history approach. GaBI. 2012;1:21-35) as well as encouraging INN prescribing (as seen in the UK, encouraged in France and a number of other countries), etc. INN prescribing would help reduce patient confusion when they are dispensed different branded generics on different occasions. However, do need robust processes for ensuring good quality generics before implementing such policies as well as educational campaigns with physicians and patients. The pharmaceutical industry may not like such approaches – but good from a patient safety viewpoint!

- Finally, may be good for the authors to compare the results of their meta-analysis of published papers regarding generics in consumers/ patients with the recently published meta analysis of Ablasheedy, Hassali et al in ‘Patient knowledge, perceptions, and acceptance of generic medicines: a comprehensive review of the current literature’. Patient Intelligence 2014:6 1–29 - to see if any papers left out, etc. (discretionary)

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 that I have no competing interests