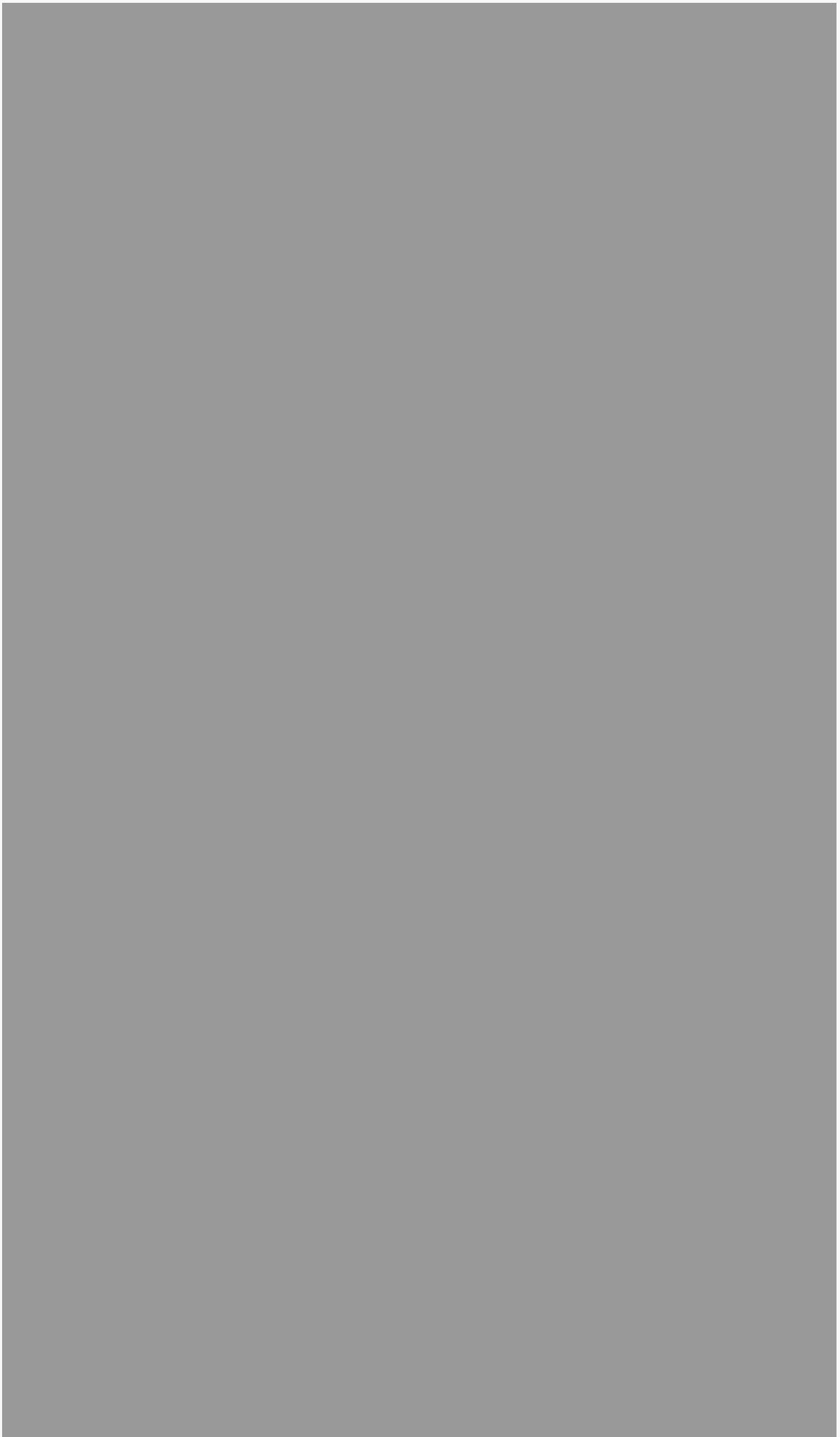

BMJ - Decision
on Manuscript
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7

**Body:** 03-Nov-2017

Dear Dr. Gaffney

Thank you for sending us this paper and giving us the chance to consider your work.

We sent it out for external peer review and discussed it at the Analysis manuscript committee meeting (present: Cat Chatfield, Peter Doshi, Navjoyt Ladher, Andrew Mataya, Emma Rourke).

Unfortunately we do not consider it suitable for publication in its present form. However if you are able to amend it in the light of our and/or reviewers' comments, we would be happy to consider it again.

The reviewers' comments are at the end of this letter.

The article was discussed at some length by the editorial team. Although, we are keen to see a revision of the article responding to the requests of the reviewers our biggest concern is that the article is substantially longer than our requirements for Analysis articles in the journal. The word limit for Analysis articles is 1800-2000 words. The current submission is 4200 words, 115 references, 7 tables, 2 figures, a panel and supplementary material.
http://www.bmj.com/about-bmj/resources-authors/article-types/analysis

As a compromise we would be able to accommodate a revision that was closer to 3300 words with substantially fewer tables and figures.

In addition to the comments raised by reviewers the editorial team raised two further concerns:

1. This is a very ambitious proposal - total reform of the pharmaceutical and healthcare systems in Canada and the United States. Given that change is not simply a technical exercise how likely is it that this could be achieved given the political context.

2. The article presents an economic analysis. Given that economic study requires substantial assumptions and calculation, we feel that this may be best presented elsewhere as an independent analysis rather than as a table and supplementary file in this article.

We hope that you will be willing to revise your manuscript and submit it within 4-6 weeks.When submitting your revised manuscript please provide a point by point response to our comments and those of any reviewers.

Please note that resubmitting your manuscript does not guarantee eventual acceptance, and that your resubmission may be sent again for review.

Once you have revised your manuscript, go to https://mc.manuscriptcentral.com/bmj and login to your Author Center. Click on "Manuscripts with Decisions," and then click on "Create a

Resubmission" located next to the manuscript number. Then, follow the steps for resubmitting your manuscript.

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IMPORTANT: Your original files are available to you when you upload your revised manuscript. Please delete any redundant files before completing the submission.

If accepted, your article will be published online at bmj.com, the canonical form of the journal. Please note that only a proportion of accepted analysis articles will also be published in print.

I hope you will find the comments useful. Please don't hesitate to contact me if you wish to discuss this further.

Yours sincerely

Paul Simpson, PhD
International Audience Editor, The BMJ
psimpson@bmj.com

**IMPORTANT INFORMATION TO INCLUDE IN A RESUBMISSION

Key messages
This is a box at the end of the article containing 2-4 single sentence bullet points summing up the main conclusions.

Instead of returning a signed licence or competing interest form, we require all authors to insert the following statements into the text version of their manuscript:

Licence for Publication
The Corresponding Author has the right to grant on behalf of all authors and does grant on behalf of all authors, an exclusive licence (or non exclusive for government employees) on a worldwide basis to the BMJ Publishing Group Ltd to permit this article (if accepted) to be published in BMJ and any other BMJPGL products and sublicences such use and exploit all subsidiary rights, as set out in our licence (http://group.bmj.com/products/journals/instructions-for-authors/licence-forms).

Competing Interest
Please see our policy and the unified Competing Interests form http://resources.bmj.com/bmj/authors/editorial-policies/competing-interests. Please state any competing interests if they exist, or make a no competing interests declaration.

Reviewer(s)' Comments to Author:

Reviewer: 1

Recommendation:

Comments:
This is a very ambitious policy document focused on US and Canadian pharmaceutical reform. I find it curious that it is submitted to the BMJ and not to a North American journal. Fundamentally I have much sympathy with many of the arguments put forward. It draws on North American literature with which I am quite familiar
The authors put forward 5 opening objectives:

1) medical needs should determine access to drugs. This begs the definition of need. Need is both a demand and a supply concept. I, as a patient may have a need even though it it is misinformed and evidence free in terms of benefit.Need is not utilisation. On the supply side need is related to effectiveness :does it improve the length and/or the quality of life?

2) drugs should be affordable to society. Throughout the submission there is a reluctance to address the issue of cost effectivenss. What institutions should use what mechanisms to ration demand . The English and the Welsh use NICE and the arbitrary cost QALY cut off of circa £30000 ( although colleagues such as Claxton et al argue an evidence based cut off would be nearer £12000 per QALY). The Scots use a different mechanism with results similar to NICE and most "civilised countries (e.g. from Germany to Thailand) use related approaches. I am aware that industry "castrated" Obama's attempt to move in this direction with PCORI but why cede consideration of this issue in this reform plan?

3) innovation geared towards maximisation of human health. Maximisation of human health from inevitably finite budgets requires "groping" mechanisms such as NICE or what American opponents call "death panels"! The work of pharmacists in the US is tackling prioritisation at the local level as industry has stymied Federal and State regulation

4) health to take precedence over intellectual property. Companies have a remarkable track record in "squeezing" patents to maximise monopoly rights and profits (e.g. Nexium). A concern must be that diluting propoerty rights would affect the volume of innovation. This is where I have sympathy with Finkelstein and Temin (2008) who suggest the separation of R&D incentivisation and the maximisation of new knowledge, and the sales and marketing of new compounds. The former could auction new compounds to competing market sellers, thereby making money to fund research independently

5) complete objective information available to prescribers and patients. Information could be improved but "compete" regardless of cost? Cancers of the breast and myeloma are hetrogeneous like the side effects for patients? Medication often means cautious experimentation with very limited evidence?

Additional comments

1) Open trials advocated so vigorously by Ben Goldsmith do seem to be having an effect on companies declaring adherence in future trials. However the problem remains of trial data from the past not being accessible to reviewers. This data is not available for meta-analyses of products in common use now.

2) The free prescriptions in Wales, Scotland and Northern Ireland and their low prices: causation not user charges but NICE? (page 8)

3) "all needed medication" : back to Archie Cochrane please (1972) (your page 8)

4) "prices should reflect actual costs of R&D, production plus a reasonable return" . How will this fund future R&D/"blue sky thinking"? Finkelstein and Temin again?

5) formulary and price competition: price discrimination may survive

6) public production: mostly failed except for Cuba? Greed and profits typically an expensive and effective (not necessarily cost effective) engine of innovation in pharma and elsewhere?

7) counter promotion: Avorn and UK attempts such as that by Nick Freemantle et al in the UK (Ebor project) show potential but this potential not exploited. Why?

8) user charges: agreed they are a tax on the ill and the means by which expenditure is switched from public to private entities

9) current propensities for competition to drive down generics' prices and "gouging" by some product owners illustrates further problems of this troublesome market that keeps me alive!

Overview
I enjoyed reading this paper: thanks! It is a stimulating and intriguing attempt to improve the efficiency and equity of the market for pharmaceuticals in Canada and the USA The pursuit of equity requires universal health provision without user charges but universalism is under threat internationally e.g the savage under-funding of the UK NHS. The pursuit of efficiency requires the development and application of cost effective criteria. Canada has a universal system with a cost effectiveness mechanism. US (bless 'em!) has Trump and a constitution imposed by French political philosphers which makes Big Pharma government at the Federal level almost impossible.At the pharmacy level and via insurers there are increasing attempts to use cost effectiveness criteria in allocating pharma funding

How could such proposals as these be implemented amongst riotous and powerful competing groups? Advocacy needs complementing with implementation plans?

In conclusion Big Pharma is rotten at the edges and needs evidence based reform. However these proposals, humane and sensible to a considerable degree, cannot ignore economic issues such as cost effectiveness and the production of innovatory products to enhance my and your QALYs!

Additional Questions:
Please enter your name: Alan Maynard

Job Title: Emeritus Professor of Health Economics

Institution: University of York, England

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

Fees for consulting?: No

Have you in the past five years been employed by an organisation that may
in any way gain or lose financially from the publication of this paper?: No

Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this paper?: No

If you have any competing interests <A HREF='http://www.bmj.com/about-bmj/resources-authors/forms-policies-and-checklists/declaration-competing-interests'target='_new'> (please see BMJ policy) </a>please declare them here: None

Reviewer: 2

Recommendation:

Comments:
This is an excellent paper, and I recommend publication. The recommendations are evidence-based and clearly explained.

I find only one shortcoming, which is that there is ample evidence of the harms produced by industry 'detailers', sufficient to justify a recommendation that such activities be outlawed. This would reduce industry expenditures by 10%-20% of revenues (see p. 33 of 57, and references 79 and 80), creating 'tax room' for a new 10-15% tax on pharmaceuticals; these revenues could be used to fund the proposed enhancements to public drug policy, and also to expand 'academic detailing', where government-sponsored representatives visit physicians in

their offices and present objective information designed to promote evidence-based prescribing.

If the authors agree with my comments, I would be happy for them to include this idea in their recommendations, with appropriate attribution.

Additional Questions:
Please enter your name: Rebecca Warburton

Job Title: Associate Professor

Institution: University of Victoria

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

Fees for consulting?: No

Have you in the past five years been employed by an organisation that may
in any way gain or lose financially from the publication of this paper?: No

Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this paper?: No

If you have any competing interests <A HREF='http://www.bmj.com/about-bmj/resources-authors/forms-policies-and-checklists/declaration-competing-interests'target='_new'> (please see BMJ policy) </a>please declare them here: I collaborated with Joel Lexchin on a research project that ended in 2011 or 2012. I think we were co-PIs. I think this is a potential rather than an actual conflict of interest; but thought I should declare it.

Reviewer: 3

Recommendation:

Comments:

This is a meaningful and comprehensive analysis of the US and Canadian Pharmaceutical System by a prestigious Reform Working Group, members of which have been long-time critics of the US drug industry--its profits, limitations in bringing truly innovative therapies to market, and its business behaviors allowed and supported by US Government and FDA regulation. In addition, a number of the authors have been long-time consumer advocates and champions and have been highly critical of the

US Commercial insurance system, advocating a single payer national solution.

We all have biases when issues of drug pricing, national drug policy and health technology assessment and value frameworks are considered. And it is critical to engage government, academic leaders, and policy leadrs in this debate, but my overarching concern is that this extremely well referenced analysis could be more balanced in highlighting some strengths of the current model, which can serve as a foundation for the "prescription for reform".

Drugs now constitute the most rapidly growing sector within health care and account for between 20-25% of total medical spending for commercial plans and in the high teens for Medicare plans. There should be a discussion of total drug spending, including biologics in addition to some of the rather dramatic cost differences cited for insulin. Table 7, I believe, does not include biological agents covered in Medicare part B and through the medical benefit for Commercial insurers. If the US spends over 500B on drugs, then these reforms, taken together at 2-3B are incredably modest, representing less than .5% of all drug spending.

The discussion of placing vital medications out of teach for many patients doesn't capture the complexity of out of pocket maxima, rebate support programs and other elements involved in drug aquisition.

There should be a discussion of the FDA Safety Sintinel System, which is a highly evolved and capable system that uses a distributed network to assess the safety of drugs post approval. This Safety Sentinel System involves 18 data partners, 193M patients and 5B prescriptions and has resulted in 70 peer reviewed papers, 48 methods reports and over 140 formal safety assessments--so to say that the safety of drugs must be independently and rigorously evaluated misses this major public private initiative.

There should be a discussion of market forces and their impact on prices for treatment for hepatitis C. While still highly costly, they are far less than their price on approval

To call the pharmaceutical industry's record on innovation desultory does not recognize emerging gene therapies, RNA therapies, agents targeted at molecular markers or treatments now available for ultra-rare diseaes, such as cystic fibrosis.

What do the authors believe is the impact of real world evidence in a transforming health care environment of big and democratized data? The RCT while a gold standard, is not the only approach to learn more about the clinical effectiveness of drugs in clinical settings--should this be an area of health system collaboration and reform?

There is a meaningful discussion of low persistence rates related to drug pricing. While drug costs may be a contributing factor, low adherence rates for therapy is far more complex and even when drugs are provided for free or very low cost, persistency rates are low.

This analysis identifies many of the issues driving high prices, including profit margins in the 15-20% range, marketing budgets that equal research and development budgets, and vastly higher prices charged in the US, but to enable readers to be more informed, the drug dollars should be followed to include the impact of rebates on net costs and the US contribution to global pharmaceutical company profitability.

A number of proposed reforms are highly intriguing including the NIH Clinical Trials Division and the NIH Drug Innovation Division. There should also be a discussion, particularly in Canada, on the impact of regulated pricing and private investment in life science companies and innovation.

While criticisms of our current drug system are warranted, the broad strokes being applied on so many fronts does a disservice to an informed debate about the strengths and challenges and the opportunities to reform our current model.

By addressing these issues, this analysis will be even more informative and serve as a foundational paper for the ongoing reform debate.

Additional Questions:
Please enter your name: Samuel Nussbaum

Job Title: Health care policy and business consultant, senior advisor to venture funds and life science companies

Institution: EBG Advisors, Sandbox Industries, Senior Fellow, USC

Reimbursement for attending a symposium?: Yes

A fee for speaking?: Yes

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

Fees for consulting?:

Have you in the past five years been employed by an organisation that may
in any way gain or lose financially from the publication of this paper?: Yes

Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this paper?: Yes

If you have any competing interests <A HREF='http://www.bmj.com/about-bmj/resources-authors/forms-policies-and-checklists/declaration-competing-interests'target='_new'> (please see BMJ policy) </a>please declare them here: From 2000-2016, I was executive vice president and Chief Medical Officer for Anthem/WellPoint. During that time, I had accountability for all pharmacy programs,

| | |
|---|---|
| | formularies and relationships with ExpressScripts, after Anthem sold its PBM to ExpressScripts. Since leaving Anthem, I have served as Chair of the Strategic Advisory Panel of the Innovation and Value Initiative, have spoken at forums regarding drug prices, have consulted with biotechnology and pharmaceutical companies, amd have served as an advisor to venture funds and policy groups. While at Anthem, I was involvd in the creation of the Campaign for Sustainable Rx Pricing. |
| **Date Sent:** | 03-Nov-2017 |