Author's response to reviews

Title: Why European and US drug regulators are not speaking with one voice on anti-influenza drugs: regulatory review methodologies and the importance of "deep" product reviews

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Author’s response to reviews:

Reviewer #1: The authors are commended for their excellent work. This manuscript is particularly important in developing countries that have limited drug regulatory authority resources.

Authors’ response: Thank you.

Comments follow:

Page 4 Line 8

Suggest that the term "giant" be replaced with a more neutral or objective term such as company, firm, or corporation.

Authors’ response: Thank you for this comment. We have replaced it with “firm”.

Page 4 Line 27

Readers have no way to determine if any group or individual is truly independent regarding potential or real conflicts of interest. Authors or groups frequently self describe their work as independent. Suggest that “independent” be removed and that determining true independence is problematic.

Authors’ response: Thank you. We have replaced “independent” with “non-industry funded”.

Page 5 Line 56

"We also propose that persistent uncertainty and knowledge deficits regarding NIs could have been ameliorated had regulators proactively engaged in a public debate".
Suggest brief mention of the FDA’s legal authority and potential political barriers to the agency participating in a public debate, presumably with other national drug regulatory authorities.

The FDA has the legal authority to determine if a sponsor has submitted substantial evidence that a drug will do what is claimed in the professional product label. The Food, Drug, and Cosmetic Act does not contain provisions that would allow the agency to participate with other national drug regulatory authorities in a public debate on the quality and methods of a new drug review. Such debates would require additional economic and personnel resources that the FDA does not have and are unlikely to have under its new administration even if it had the legal authority.

The FDA because of the Freedom of Information does provide the materials available for public debate by patients, clinicians, and policy makers in the form of freely available regulatory as were provided in this manuscript. Free publically available FDA regulatory documents may contain rigorous analyses of unpublished clinical trials and other analyses conducted by the agency.

Authors’ response: This is an important point. However, our statement that regulators should have engaged in a public debate was not intended to imply that regulators should necessarily have debated each other. Rather, what we are suggesting – and as we develop further in the discussion – is that if regulators, and especially the FDA, had effectively disseminated their gained knowledge about the qualitative and statistical facets of NI trials alongside their methodological deliberations, this would most likely have improved the synthesis and critical appraisal of the clinical evidence by the broader medical community. We have clarified in the abstract, introduction and discussion that our point is that regulators should have “engaged in the public debates over the drugs’ efficacy” - i.e., not that they should necessarily have debated each other.

Importantly, regulators – and especially the FDA – recurrently engage in public (including professional-scientific) debates; and FDA top management (see Discussion) have emphasised that “Establishing the FDA as a public health agency requires a culture that encourages scientific exchange.” This shows that there are no definitive legal, political or economic barriers at play – even though, as the reviewer points out – the FDA would definitively need additional economic and personnel resources to accomplish what we are suggesting. For debates or commentary regarding specific products or drug classes involving the FDA or MPA, see e.g.:


Page 6 Line 39

A brief definition of "grey literature" may be helpful that includes publically available drug regulatory authority documents.

Authors’ response: We have added “e.g., government or public body reports” to include both drug regulatory authority documents and public body evaluations and statements, such as those produced by NICE and the Public Accounts Committee in the UK and the CDC in the US.

Page 15 Line 36

"… but see authors, forthcoming". See no additional reference to this statement. Is there a plan for an additional study?

Authors’ response: Yes, this is a forthcoming, submitted study in which we use publically available correspondence between FDA and the company to analyse how and why FDA staff and management circumvented the negative opinions and recommendations on Relenza expressed by DAVP reviewers and its Advisory Committee. The forthcoming paper highlights contradictions between a scientific culture existing within the FDA, conducive to rigorous product evaluations (as shown in the present study), and the agency’s attempts to accommodate political and corporate interests.

Page 19 Line 12

The -0.25 day point estimate does not appear in Table 1.

Authors’ response: We are very grateful for this comment. We have updated Table 1 to include results from the HR-IP subgroup from all three trials - including the -0.25 day point estimate in the NA study.

Page 30 & 31 Lines 51 -10

See comments for Page 5 Line 56. In addition to legal authority for the FDA and international drug regulatory authorities is the transparency of drug regulatory authorities outside
the FDA. Do other international authorities allow access to drug reviews similar to Sweden and the US?

Authors’ response: Please see our response above. Regarding the question if other agencies allow access to drug reviews, we believe this is beyond the scope of present paper to address. We would think that the FDA and MPA were (and possibly still are) more transparent than many other drug regulators – but to confirm this we would need to carry out a separate study.

Page 33 Line 7

FDA regulatory reviews are required to be made publicly available by law for years. Medical reviewers, journal editors, and clinicians must accept some responsibility for the under utilization of these documents.

Authors’ response: Thank you. This is a very good point and we have included it in the manuscript.

Reviewer #2: This is a very important, topical well written and well researched piece of work on Relenza, the NI which traditionally has received less attention. The points the authors make are valid and their importance lies in the disparity between thoroughness of reviews carried out by the two regulators.

I only have one comment. I can suggest some of the reasons behind the Zanamivir licensing decision and the sense of panic that permeated GSK when they were struggling to convince FDA that the drug was not the dud it is.

The Drugs@FDA files:

Tamiflu and Relenza/Relenza/Relenza - NDA 021036/19990726_000/021036-admin1.pdf

Tamiflu and Relenza/Relenza/Relenza - NDA 021036/19990726_000/021036-admin2.pdf

contain correspondence and memos from and to FDA and GSK (in particular Heidi Jolson of CDER and Sherman Allfors of GSK). They may also consider citing the GSK offer of ditching the whole Canadian dataset (second file, page 8 of pdf, record of meeting held on 1/7/99).

I look forward to reading the paper in print.

Best wishes,

Tom.
Authors’ response: Thank you Tom for the kind words and the suggestions. Why the FDA approved Relenza despite the negative opinions is clearly a key issue but one - we have found - that requires a separate paper to explain. Indeed, in a forthcoming, submitted study we do exactly what is suggested. Based on detailed reading of the correspondences and memos, we show that FDA staff and management helped GW by guiding its analyses and by participating in constructing a tenuous argument for approval. A key component of the FDA’s strategy was finding “the most generous statement justifiable” regarding efficacy to print in the product label. The forthcoming paper highlights contradictions between a scientific culture existing within the FDA, conducive to rigorous product evaluations (as shown in the present study), and the agency’s attempts to accommodate political and corporate interests.