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Title	Hormonal contraception regulatory approval time in Canada, the United States and the United Kingdom 2000 to 2015, a retrospective data analysis
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Reviewer 1	Dr. Nigel Rawson
Institution	Eastlake Research Group, Oakville, Ont.
General comments (author response in bold)	My main reservation regarding this manuscript is in the analysis. 1. The numbers of products in each country is small and the distributions of the approval times are right-skewed (see Figure 2), i.e. not normally distributed. However, the authors assume that the data are normally distributed and use means and standard deviations to summarize the data and F-tests to analyze them when they should, in my opinion, be using non-parametric statistics. **Response: Thank you for noting this limitation. We've redone the analysis using non-parametric tests and are careful to acknowledge the small sample size.** 2. In addition, Figures 1, 3 and 4 show box plots with the boxes showing the interquartile range and the "whiskers" showing what the authors' call the minimum and maximum values. However, the authors also show "outliers" beyond the minimum and maximum values that are not defined in the manuscript. In Figure 1, there are apparently 3 outliers out of the 16 products approved in Canada; this means that close to 20% of the Canadian approved products are considered outliers, which raises the questions of why and what are they? **Response: Good points. The figures have been redone to show the spread of data. The identity of the outliers in Canada has been stated in the text.** 3. I suggest that the authors consult a qualified statistician to review their analysis and demonstrate why they exclude data. **Response: Revised entirely, as suggested. Thank you for this excellent suggestion**. 4. Finally, the manuscript could be shortened, especially in the Introduction and Discussion. Intellectual on page 7 is spelt incorrectly. **Response: Thank you for your helpful comments, Dr. Rawson. We have also shortened the manuscript.**
Reviewer 2	Dr. Susan Wood
Institution	George Washington University, Health Policy and Management, Milken Institute School of Public Health, Washington, DC
General comments (author response in bold)	This study raises an important question about the rate of approval of contraceptive products through 3 leading regulatory agencies; Canada, the US and the UK. The methods to assess the time from submission to decision seem appropriate with some limitations. However, it does not include information about the time that the application is turned back to sponsors when the regulatory body is seeking additional information. Total approval time is not always due to regulatory review time. The most clear comparison in Table 2 provides product specific data which is the most direct comparison of approval times. Combining products to compare as a whole, is less informative unless similar analysis is done for other classes of products (see below). There is other key information which is lacking from the manuscript. 1. There needs to be discussion about the range of differences and different barriers for each regulatory agency, ranging from approval process, is the agency working under legal deadlines, what are the resources (staff) available to each agency, do they evaluate original data, etc? The reader may not be familiar with the key differences in the different country regulatory schemes. This information should be included in both the introduction and discussion. **Response: Good point. Thank you for these excellent suggestions! We have added further key information about the regulatory and approval processes within each of the countries. As per the request of Reviewer #1, we tried to keep our manuscript short and to do so limited the detail we could include addressing this point. Here is the new paragraph we have provided to summarize the key factors:** **The differences in approval times between countries may reflect a range of contextual conditions. For example, prior to 1992, Canada and the US had similar lengths of drug approval times [44]. The implementation of the Prescription Drug User Fee Act in 1992 [45] saw the shortening of the US drug**

	approval times. This act allows for the collection of fees from the pharmaceutical companies and thus allowed the FDA to speed up the approval process. Requiring a fee appeared correlated with a shorter approval time [46]. In 1995, Health Canada's Therapeutic Products Program reduced their approval time from 1057 days to 650 days by processing the excess submissions [46]. As of April 2016, Health Canada required manufacturers to pay a higher but variable fee, depending on the presence of a new active substance [47]. The MHRA requires a much smaller fee payment for new applications of drugs containing an active substance, in the range of 5-10% of the fees of HC [48-9]. Conversely, the FDA requires a fee more than 10 times that of HC for a new drug application with clinical data [45]. The large differences in fees between the three countries may be due to variety of factors, including the size of the market for the product within the country. 2. There also needs to be information on whether this difference in approval times is different for contraceptive products or similar for all product reviewed in the different countries. This may require a separate comparative group of products or use of already existing studies comparing approval time across multiple products. The authors presume that this is specific to or exacerbated for contraceptive products (which may be true) but there needs to be some comparison and discussion about overall approval times across product classes. [Editor's note: This could be accomplished by comparing your results with the results of Downing et al. in the Interpretation section] **Response: Thank you for your comment Dr. Wood. We approached the regulator agencies for information on applications that were turned back to the sponsors, however they will not release this data as it is deemed confidential. All of our statistics, figures and tables have been redone to more accurately represent approval by the three agencies. We did not include a comparison chart with Downing et al, as these authors included a different set of regulatory agencies (in particular with no information the MHRA).** With the addition of the information above, I think this manuscript could add important information for researchers, clinicians and policymakers in Canada and beyond. **Response: Thank you for your support of the importance of this manuscript!**