Reviewer’s report

Title: Immunogenicity and safety of inactivated quadrivalent influenza vaccine manufactured using a thimerosal-free process with thimerosal added during formulation for multidose presentation

Version: 1 Date: 5 December 2013

Reviewer: Joanne Langley

Major Compulsory Revisions

This is described as a non-randomized study of two inactivated influenza vaccines to determine safety and immunogenicity in two adult age groups. The study appears to be open-label, unblinded, observational study of two different vaccines given in successive years.

The purpose of the study is to demonstrate that the addition of thimerosal at a different point in the manufacturing process does not alter its immunogenicity or reactogenicity.

1. The title does not indicate that the study aims to make a comparison, as is indicated in the last sentence of the introduction, nor does it indicate the age group.

2. The brand name of the products and the sponsor appear multiple times in the manuscript. It would be preferable to use a generic name. In the Vaccine section when the vaccines are described the sponsor and brand names could be mentioned once for identification.

3. The abstract methods refer to “spontaneous adverse events”; later the paper uses the more common terminology “unsolicited AE”. The term spontaneous adverse event is usually refers to spontaneous passive reporting of products that are licensed and in use.

4. Introduction. All licensed US QIVs should be mentioned, not just those of the sponsoring company.

5. The rationale of “reduced demand on cold chain storage systems” should be explained, since vaccines with or without thimerosal need refrigeration. Do you mean that a multidose vial would take less space?

6. Regarding rationale, this is best described in a sentence in the discussion p. 11 “As this process change could have affected the immunogenicity of the product, we conducted the current study.”; it is suggested that this be brought to the introduction.

7. Methods. Some study design details are missing. Indicate that allocation and observations were unblinded, if this is the case. Participants were in stable health; could they have chronic illnesses which were stable?

How many doses are in the multidose vial?
8. The study was conducted at one site in Canada which is not identified, but has an Institutional Review Board. Were the regulatory requirements mentioned in the last line of page 4 those of Canada?

9. Page 6. “In the TIV and QIV studies, the secondary objective…” The wording is awkward here, and implies that there were other studies than the TIV and QIV. Was reactogenicity, with two outcomes, a secondary objective? In the next paragraph a different objective (evaluate unsolicited events) is stated to be the secondary objective. Please clarify.

10. Analyses. Is the sample size requirement for Canada or Europe (since CHMP outcomes were used)?

11. Page 7, last paragraph of analyses section. Does “at a given time point” refer to both the day 0 and day 21 serology?

12. Results, page 7. “…all of which completed;” – completed the study?

13. Regarding discussion of prior vaccination, it should be noted that Canada used an oil-in-water (AS03) adjuvanted pandemic influenza vaccine in 2009 (Table 1, or in the text).

14. The frequency of injection site pain is quite high in the 18-60 year olds (73 – 82%) and deserves some comment. Local AEs were collected for only four days. Was pain resolved at four days in these participants?

15. The phrasing regarding the association between prior influenza vaccine and immune responses in the study is such to imply causation, “…previous vaccination reduced immune responses…” Causation cannot be concluded from this evidence. It would be preferable to note the association without implying causation.

16. Two serious AEs occurred. Was the Crohn’s disease really of new onset in the 21 days after vaccination? Please note spelling of Crohn’s.

17. The discussion could be shortened by reducing the repetition of results.

18. Re contributorship the person that drafted the articles is not indicated (ICJME guidelines).

19. Figure Subject flow. Please add the years each study was done, ie column one 2010-2011, and over column two 2011-2012.

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

My institution (Dalhousie University) has received funds for the conduct of research studies from the sponsor (GlaxoSmithKline Biologicals (GSK)).
I have been a co-investigator on vaccine studies with the authors of this paper.

My institution has received funds for the conduct of vaccine studies from sanofi pasteur, Novartis, Pfizer, Merck,

I am the current holder of an endowed chair in Pediatric Vaccinology that is co-funded by the Canadian Institutes of Health Research (CIHR), GSK, the Dalhousie Medical Research Foundation, the Department of Pediatrics at Dalhousie University, Associated Pediatrics Incorporated, and the IWK Health Centre.