Reviewer's report

Title: Evaluation of non-inferiority of intradermal versus adjuvanted seasonal influenza vaccine using two serological techniques: a randomised comparative study

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Reviewer: Ralf Wagner

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Summary of the work:

The authors report on the results of a clinical study that was undertaken in an elderly population to compare two different forms of trivalent seasonal influenza vaccine. The following vaccine products with a strain composition for the 2007/2008 northern hemisphere season have been applied:

- a MF59 adjuvanted subunit vaccine containing 15µg of HA per strain in a dose volume of 0.5ml for intramuscular application (Fluad®, licensed for use in certain EU countries in 1999)
- a non-adjuvanted split virion vaccine containing 15µg of HA per strain in a dose volume of 0.1ml that is applied intradermally by means of a specifically designed device (Intanza®, licensed in the EU in 2009)

One aim of the study was to compare vaccine efficacy according to the criteria established and applied by the European medicines agency for seasonal and also pandemic vaccines. These include seroprotection, seroconversion and rise in GMT measured by either HI- or SRH-test to quantify the HA-specific antibody response.

Another aim was to explore the safety profile of the two vaccines by assessing both local and systemic adverse reactions.

Based on their data the authors conclude that the intradermally applied vaccine is “not inferior” to the intramuscular vaccine with respect to immunogenicity and safety aspects.

Comments:

The aim and design of the study are well chosen. Given the decreasing activity of the aging immune system (“immunosenescence”) it is indeed an important question how vaccination efficacy against seasonal influenza in an elderly population can be improved. One option is to include powerful adjuvating components into the vaccine formulations. The applicability of such an approach has been confirmed recently for seasonal as well as for pandemic vaccines. Another alternative might be the use of novel routes of administration, such as intradermal application. In the present study these two vaccination strategies have been compared by analysis of HI- and SRH-results (that primarily determine the antibody response directed against the HA protein) for compliance
with the CHMP immunogenicity criteria. In principle this is regarded a reasonable procedure since these are the pivotal (and well established) criteria commonly applied for influenza vaccine efficacy determination and hence the data generated are very valuable in regulatory terms. However, it is felt that a couple of specific issues should be addressed by the authors:

- Since the intradermal application is a very novel mode of administration it would be crucial to have a broader view on the immune response elicited by this route – in particular since for the adjuvanted vaccine counterpart such information (eg cytokine stimulation profile, immunity to drift variants…) is available. This is quite an important issue since such immunological effects could have a pronounced impact on the boosterability of immunogenicity induced by annual vaccination and hence on the medium and long-term efficacy of the vaccine. Due to their involvement in the licensing procedure for Intanza® the authors most probably have access to such data on the activation of different arms of the immune system in response to vaccination. Reference should be made to these data to support the authors’ claim of comparability and/or equivalence of the immunogenicity profile of the two vaccines.

- Next, the definition of “non-inferiority” (upper limit of 95% CI # 1.5) as implemented by the authors needs further justification. From the data provided it is clear that the GMTs achieved with the adjuvanted vaccines are somewhat higher and it is at current difficult to conclude/predict whether this has any impact on vaccine efficacy or not. Therefore, more information on the scientific rationale for setting the limit to 1.5 should be provided.

- Further, more detailed information on the pre-immune status of study participants is urgently required. It is most likely that especially in the elderly population there is a significant level of seroprevalence against seasonal influenza strains. In the manuscript it is stated that such “baseline antibody titers were slightly different in the two groups”. This is an important point since any bias in seroprevalence before vaccination can have a drastic impact on titers achieved by vaccination. The authors need to clarify this point appropriately. In this context, the procedure followed for the “post-hoc ANCOVA adjusting for baseline” titers shall be described in more detail.

- Lastly, although all safety signals that have been detected are rather mild it is clear from the presented results that injection site adverse events were more frequent with the intradermally administered vaccine. Hence the two vaccine preparations are not fully equivalent in this respect. Therefore it might be reasonable to clarify that the two vaccines do not have exactly the same safety profile but that the higher rate of injection site reactions is acceptable due to the mild symptoms and the short duration.

**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:
I declare that I have no competing interests