Comments from **PowderMed Ltd**., The Oxford Science Park, Oxford, OX4 4GA, UK

Draft Guidance for Industry
Clinical Data Needed to Support the Licensure of Pandemic Influenza
[Docket No. 2006D-0088]

General Comments

As written, the guideline describes development approaches that are stated to be applicable to the following pandemic influenza vaccines:

1. "Split" and whole virus inactivated vaccines propagated in chicken eggs.
2. Cell-culture derived
3. Recombinant hemagglutinin-based protein
4. Adjuvanted
5. Live attenuated

The guideline explicitly does "not address influenza vaccines that do not contain a hemagglutinin component".

The vaccines listed under1 to 3 above, all function by introducing hemagglutinin (HA) into the body, leading to a humoral immune response that results in the production of HA antibodies. Potency of these products is normally assessed by measuring the level of these antibodies.

A novel approach to influenza prophylaxis is the use of DNA plasmid vaccines that contain the hemagglutinin (HA) gene. These vaccines cause the recipient's cells to produce HA *in situ*, which is then able to induce an HA antibody immune response in a manner analogous to that described above. As the HA is produced within the cell, it also has the potential to additionally produce a cell-mediated immune (CMI) response. While the role of such a CMI response in influenza prophylaxis is unclear, it is reasonable to assume that it would have a neutral to positive effect on protection (i.e. it is improbable that it would have a negative effect). In any case, the induction of an additional cellular response should have no negative impact on the usefulness of hemagglutination inhibition

(HAI) titres as a surrogate predictor of efficacy for HA-expressing DNA vaccines. If a DNA vaccine produced an HA immune-response equivalent to a product listed under 1 to 3, it is difficult to see why it would be less effective in preventing influenza. Furthermore, given the toxicology and human safety data already generated and provided to the FDA, there should be no reason to expect that HA based DNA vaccines present any significantly greater safety risks compared to other new technologies such as cell based or recombinant HA. The safety database required in this guideline for these technologies should thus also suffice for the adequate determination In the areas of both efficacy surrogates and safety profiling, this guidance should thus be sufficient for HA based DNA vaccines as well as for other HA based vaccines.

A recent Phase 1 study of an H3 DNA influenza vaccine, conducted in the US, produced an HA antibody response of a magnitude required for the registration of annual influenza vaccines in the European Union[1].

Given a common (HA-mediated) mechanism of action, and proven ability of a DNA vaccine to produce an immune response of similar magnitude to registered influenza vaccines, it seems appropriate that the guideline would also cover HA-expressing DNA vaccines.

It is also important that DNA vaccines are not disadvantaged relative to older technologies. DNA vaccines offer a number of actual and theoretical advantages over alternative technologies, and have the potential to be an important component of pandemic preparedness. Such advantages include:

- Speed and certainty of production.
- No requirement for eggs.
- No biocontainment hazard (no live virus used in manufacture).
- Stable at room temperature over a prolonged period.

As currently written, it is not clear whether an HA-expressing DNA vaccine would be included under the scope of the guideline. Based on the above considerations, we recommend that the guideline is modified to explicitly include HA-expressing DNA vaccines within its scope. The detailed comments (below) identify areas where clarification would be helpful.

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[1] Drape RJ, Macklin MJ, Barr LJ, Jones S, Haynes JR, Dean HJ (2005). Epidermal DNA vaccine for influenza is immunogenic in humans (Submitted for Publication).

Page/Section/Para	Original Text	Comments
Page 1/I/ Para 1	"The approaches apply to "split virus" and whole virus inactivated pandemic vaccines propagated in embryonated chicken eggs, and are also applicable to cell-culture derived, recombinant hemagglutinin-based protein, and adjuvanted pandemic influenza vaccines. "	It is not clear whether the guideline applies to DNA vaccines. Many of the principles of the guideline could be applied to facilitate the development of a pandemic DNA vaccine. Conversely, DNA vaccine development and their sponsors would be disadvantaged if this guideline does not apply. Given the proven limitations of protein antigen pandemic vaccines (Section 3.D), it is important that that promising novel approaches are supported. We suggest that the text is revised to explicitly include DNA vaccines that endogenously produce hemagglutinin.
Page 1/I/ Para 1	"This document does not address influenza vaccines that do not contain a hemagglutinin component"	DNA vaccines that function by producing hemagglutinin endogenously should be considered to "contain a hemagglutinin component" and should not, therefore, be excluded from the scope of the guideline.
Page 9/C.3.a	"Confirmatory studies if a sponsor pursues U.S. licensure of an annual TIV vaccine"	The previous text of Section C does not make specific reference to *inactivated* vaccines. Suggest that this is reworded to "…..an annual trivalent vaccine"
Page 9/C.3/Para 1	"Sponsors seeking approval of a pandemic influenza vaccine strain are encouraged to pursue development of a trivalent inactivated influenza vaccine using the same manufacturing process as used for the pandemic influenza vaccine"	If a pandemic vaccine may be approved in isolation (i.e. in the absence of an approved trivalent product) it would be helpful to state this explicitly.

Page 10/D.1	"The recommendations in section III.C. above, regarding clinical data to support the accelerated approval of a pandemic vaccine, apply to "split virus" and whole virus inactivated pandemic influenza vaccines propagated in embryonated chicken eggs. The recommendations also apply to licensure of cell culture derived, recombinant hemagglutinin-based and adjuvanted pandemic influenza vaccines"	Initial clinical data with DNA influenza vaccines, suggests a similar HI antibody response to that seen with protein vaccines. Accordingly it would seem appropriate that the term "recombinant hemagglutinin-based….vaccines" includes HA-expressing DNA vaccines. If DNA vaccines are included it would be helpful to state this explicitly.