European Medicines Agency

London, 22 January 2009
Doc. Ref. EMEA/CHMP/BWP/481473/2008

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

CONCEPT PAPER ON THE NEED TO UPDATE THE CURRENT ANNEX GUIDELINE ON CELL CULTURE INACTIVATED INFLUENZA VACCINES WITH RESPECT TO THE DERIVATION OF CELL-ISOLATED INFLUENZA VACCINE VIRUSES

AGREED BY BIOLOGICS WORKING PARTY	10 December 2008
ADOPTION BY CHMP FOR RELEASE FOR CONSULTATION	22 January 2009
END OF CONSULTATION (DEADLINE FOR COMMENTS)	30 April 2009

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KEYWORDS	Cell culture inactivated influenza vaccines, cell-isolated influenza vaccine viruses

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1. INTRODUCTION

Human influenza virus surveillance is undertaken by the WHO Global Influenza Surveillance Network (GISN) which comprises 122 National Influenza Centres (NICs) in 94 countries and 4 WHO Collaborating Centres (CCs) in USA, UK, Japan and Australia. Many of the influenza viruses isolated by NICs are sent to one of the four CCs for detailed characterisation and an understanding of the wider epidemiological situation. The resulting information is collated and used on an annual basis in recommending influenza seasonal vaccine candidate viruses, once for the northern hemisphere and once for the southern hemisphere.

A few decades ago, most surveillance laboratories used embryonated hens' eggs for isolation of human influenza viruses; nowadays virtually all laboratories make use of tissue culture cells e.g. MDCK cells are commonly utilised for isolation from clinical specimens.

Cells in use by NICs and CCs for virus isolation are not validated for human vaccine production and so currently (and this has always been the case) only egg-isolated viruses are used as potential vaccine candidates. It was understood that the egg will 'filter out' many potential human viral contaminants from the clinical specimen and would not introduce any further mammalian viral contaminants.

Because of this gradual switch over the years from isolating virus in eggs to the use of cells, when a particular virus is determined by WHO to be the recommended strain for vaccine production, there is now a need to search for an 'egg only' isolate with antigenic characteristics of the recommended strain. This is being achieved by re-isolating virus directly in eggs from a clinical specimen from which a relevant virus has been isolated in cells. This does not always work and in the early 2000's, a failure to isolate a recommended H3N2 virus in eggs resulted in the WHO resorting to recommending continued use of the previous year's strain with a resulting loss in efficacy for that season's vaccine.

Upon identification of suitable egg-derived candidate vaccine viruses, high growth reassortants (for type A influenza virus) are developed by co-infection of eggs with the recommended egg-derived vaccine strain and the high growth parental strain PR8.

In summary, any virus that has a 'cell' passage history is deemed unsuitable as a candidate vaccine virus because the cells used by surveillance laboratories are not qualified for human vaccine manufacture and there is a precedent that all viruses used in vaccine production, including cell-based production, have been passaged only in eggs.

2. PROBLEM STATEMENT

Many influenza vaccine manufacturers are developing cell culture processes for the production of inactivated vaccine using a variety of cell types and three such vaccines have been licensed within the EU (two nationally and one centrally). Currently, manufacturers of cell-derived vaccine use the egg-derived candidate vaccine virus to derive their seed virus; typically for the H1N1 and H3N2 strains, this is a high growth reassortant (hgr). There is no evidence that the use of an hgr provides any growth advantage in cells compared with the wild type egg-derived recommended strain – it is simply the vaccine virus that is available from WHO collaborating laboratories that supply such viruses – although one manufacturer of a cell-derived vaccine plans to use the wild type egg isolates.

Manufacturers of cell-derived influenza vaccine would now like to use a cell-only passaged virus and not one that has been egg-adapted. There is however no guidance on the quality requirements for cells that are used in isolating the virus from clinical material nor on tests that should be applied to the isolated virus.

3. DISCUSSION (ON THE PROBLEM STATEMENT)

Research over many decades indicates that when a human influenza virus is adapted to grow in eggs, it undergoes phenotypic changes that might include changes to its antigenicity/ immunogenicity. In the 1980's the molecular events surrounding egg-adaptation were uncovered.

Passage of a non-egg adapted human influenza virus in eggs selects for a variant virus from the quasi-species population which has a single amino acid substitution in the HA molecule adjacent to the receptor binding site of the HA; this essentially alters the receptor specificity of the virus from 'human' to 'avian' and allows the virus to grow efficiently in eggs. Depending on the nature and location of the HA amino acid substitution during egg-adaptation the antigenicity/immunogenicity of the virus might also be affected. The extent to which this occurs during egg-adaptation of candidate vaccine viruses is currently monitored by the WHO CCs to avoid significant antigenic changes to the virus.

Manufacturers are now keen to use non-egg adapted viruses for vaccine manufacture in order to use the most antigenically relevant virus for vaccine manufacture, i.e. the one antigenically most like the wild type virus. Virus isolated on cells does not undergo the type of selection that occurs during initial passage in eggs and typically the HA of a cell isolated virus is structurally and antigenically identical to the virus found in clinical material. Thus there are sound clinical reasons for preferring a cell-derived vaccine virus.

As described above, the viruses derived by NICs and CCs on cell culture cannot be used for vaccine manufacture. Also, it is wholly impracticable for each NIC to isolate wild type viruses on cells that have been validated, for example to Ph. Eur. requirements, following an appropriate quality system. To overcome this, arrangements are being tested whereby CCs will re-isolate relevant viruses from clinical material in cells provided by vaccine manufacturers under a quality system. Such a project is currently being undertaken at the USA CC at CDC in Atlanta. Industry via the IFPMA is also investigating whether the nature of the cell used for isolation has any effect on the nature/quality of the virus thus isolated.

The Annex guideline for Cell Culture Inactivated Influenza Vaccines (CPMP/BWP/2490/00)[1] provides the following information:

- Section 3.1 states that mammalian cells can be used to isolate the candidate vaccine virus.
- Section 3.2 states that the vaccine seed and production virus must be tested for relevant contaminating agents.
- Section 3.3 addresses the cells being used for vaccine manufacture.

Thus the guideline does not provide guidance for the cells being used for isolation of the virus, the conditions under which the viruses are isolated and subsequent passage of these viruses until the seed is prepared under GMP conditions.

4. RECOMMENDATION

It is recommended that the CHMP/BWP updates the current Annex guideline for Cell Culture Inactivated Influenza Vaccines (CPMP/BWP/2490/00) with respect to the issue described above, i.e. that the cells used to isolate virus destined to be used in the manufacture of human vaccine are fit for purpose. This could be achieved by the development and ultimate publication of a short appendix to the current guideline addressing these points.

The Annex guideline should also be checked through for any other necessary updates in light of experience with cell-derived inactivated influenza vaccine.

5. PROPOSED TIMETABLE

Development of this appendix should not be unduly laborious and so it is proposed that a draft suitable for external consultation be developed for publication by Q2 2009, followed by a 3 months consultation period.

6. RESOURCE REQUIREMENTS FOR PREPARATION

The appendix can essentially be developed by the BWP. This can be achieved via emails, by Vitero conference sessions and during plenary meetings of the BWP. Face-to-face meetings of the drafting group should not be required.

7. IMPACT ASSESSMENT (ANTICIPATED)

This appendix will provide essential guidance to influenza vaccine manufacturers and to WHO Collaborating Centres on the quality issues associated with cells used to isolate virus to be used in vaccine manufacture. This will streamline the development of cell-derived influenza vaccines and further assure the safety of these vaccines.

8. INTERESTED PARTIES

Internal: BWP

External: Vaccine manufacturers, World Influenza Centres and contract testing laboratories.

9. REFERENCES TO LITERATURE, GUIDELINES ETC

1. Cell Culture Inactivated Influenza Vaccines. Annex to note for guidance on harmonisation of requirements for influenza vaccines (CPMP/BWP/214/96). (CPMP/BWP/2490/00) http://www.emea.europa.eu/pdfs/human/bwp/249000en.pdf