Final Concept Paper
M6: Guideline on Virus and Gene Therapy Vector Shedding and Transmission
dated 26 August 2009
Endorsed by the Steering Committee on 18 September 2009

Type of Harmonisation Action Proposed

This concept paper sets out a proposal for a harmonized ICH guideline on Virus and Gene Therapy Vector Shedding and Transmission. The purpose of the proposed guideline will be to provide recommendations to industry and regulators on non-clinical, and clinical studies and guidance on use of analytical assays for the detection and characterisation of shed virus. It is intended that this guideline will also provide recommendations on how to use and interpret non-clinical data in order to determine whether or not virus and gene therapy vector shedding studies are necessary. The assessment of shedding can be utilized to estimate the likelihood of transmission of virus and gene therapy vectors to third parties, such as healthcare workers and family members.

Rationale

Although the Gene Therapy Discussion Group has just finalized an ICH Considerations paper on viral vector Shedding, this document focuses on general principles regarding virus and vector shedding and does not provide detailed information on this topic. The guideline will provide more extensive information that will improve harmonisation between the regions, help industry and regulators avoid unnecessary and/or uninformative studies and result in more efficient and cost-effective development of virus and vector shedding and transmission studies.

Statement of the Perceived Problem

This topic is important because gene therapy clinical research has become global. Most vectors are administered directly to patients. Depending on the virus or gene therapy vector used, the likelihood of shedding could be increased. The use of wild type viruses and gene therapy vectors that are replication- competent or have the ability to persist in patients for extended periods of time are becoming more prevalent for the treatment of many cancers and rare diseases. Although results from these studies are limited there are examples which demonstrate that these virus/vector products can be shed in patient excreta and in some cases, shedding occurs for extended periods of time. In addition, some, but not all human-to-human transmissions resulting from shedding may have adverse or unacceptable consequences. Therefore the potential for of human-to-human transmission resulting from shedding is an important public health matter. An ICH guideline would provide harmonized guidance on the design of shedding studies, avoid unnecessary and/or uninformative studies and result in refinement and a relevant reduction in the numbers of experimental animals used in non-clinical studies, as well as cut costs and create a more efficient development process. This would help industry and regulators in assessing the results of shedding studies which could be important with regard to determining acceptable benefit-to-risk profiles.

Issue to be Resolved

Depending on the virus and gene therapy vector used for treatment, shedding can occur through patient excreta after administration. In general, most viral/vector products currently under investigation are replication- incompetent or conditionally replicative and shedding of these products would be expected to be of a shorter duration depending on route of administration compared to the route of infection by a wild type virus. Currently, there is limited data available on virus and gene therapy vector shedding: and what data is available is difficult to interpret as the

studies have not been conducted in a well controlled manner, and analytical methodologies used are not standardized. Harmonisation of practices would therefore aid industry and regulators in terms of both the assessment of whether non-clinical or clinical shedding studies are appropriate and the design of any studies to be undertaken. Information gathered during development will also be beneficial when developing pharmacovigilance and risk management programs for clinical use following marketing authorisation. Issues for harmonisation will include the following:

- Information regarding the known route of infection/transmission of the wild strain virus and general biological properties of the virus/vector;
- Guiding principles for the optimisation of analytical methods that are used to detect and characterize shed virus/gene therapy vectors i.e., sensitivity, specificity, addressing sample interference, and quality of samples;
- Guiding principles for designing and conducting appropriate, controlled and scientifically sound non-clinical studies;
    - important protocol elements, selection of animal species, use of disease models, route of administration, sample types, sampling frequency & duration, impact of virus/vector type;
    - use and interpretation of non-clinical data;
- Guiding principles for clinical shedding studies;
    - timing of studies during product development;
    - study design, including number of subjects, sample types and frequency;
- Transmission – likelihood and potential consequences.

Scope

For the purpose of this ICH guideline, shedding is defined as the dissemination of the virus/vector through secretions and/or excreta of the patient. Virus/vector includes gene therapy vectors and oncolytic viruses. This ICH guidance will focus on recommendations for analytical methods, non-clinical studies, and clinical studies to support the development of oncolytic viruses and gene therapy products, and would also consider the likelihood and potential consequences of transmission.

Background to the Proposal

See appendix I for attached ICH Considerations document.
See appendix II for attached publication by *Schenk et al. 2007*.

Type of Expert Working Group

We recommend establishment of an Expert Working Group (EWG) which includes representatives/experts of the six ICH parties and observers from Health Canada, EFTA, WHO, and others on request. We suggest that based on the extensive scientific, regulatory and development expertise that already exist within the Gene Therapy Discussion Group (GTDG) that this group be considered as the experts that make up the EWG for this proposed guideline. Having the EWG consist of the current GTDG expertise would streamline the process of guideline development as well as provide for practical impact and cost effectiveness.

Timetable

The proposed EWG should be established prior to the ICH meeting in Fall 2009. The proposed EWG should meet at the ICH meeting in Fall 2009, Spring 2010 and should target the delivery of a *Step 2* document in Spring 2011. Existing and in progress ICH safety and clinical guidance as well

as existing and draft guidance, of the MHLW, FDA, and EMEA, will be consulted as the initial framework.

Parties Making the Proposal

The GTDG proposed this issue after having developed an ICH Considerations on the topic at the June 2009 meeting. All parties supported the development of a guideline on this topic.