Final Business Plan
M6: Guideline on Virus and Gene Therapy Vector Shedding and Transmission
dated 27 August 2009
Endorsed by the ICH Steering Committee on September 18, 2009

1. The issue and its costs

1.1 What problem/issue is the proposal expected to tackle?

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 different regions are aware of examples of vectors with unexpected shedding profiles although there is limited data available on virus and vector shedding. 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 is 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. Therefore, the potential for human-to-human transmission resulting from shedding is an important public health matter. The purpose of the proposed guideline will be to provide recommendations to industry and regulators on non-clinical, and clinical shedding 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. A guideline would help the field develop better benefit- to- risk profiles by identifying criteria that can be used during product development to assess the likelihood and potential consequences of shedding and transmission. Information gathered during development will also be beneficial when developing pharmacovigilance and risk management programs for clinical use following marketing authorisation. The ICH Considerations on virus and vector shedding released in June 2009, which addresses the general principles to be considered when designing non-clinical and clinical shedding studies, constitutes a first step, paving the way for a harmonized guidance.

1.2 What are the costs (social/health and financial) to our stakeholders associated with the current situation or associated with "non action"?

Harmonisation is necessary to avoid an inconsistent approach across regulatory jurisdictions that could have an impact on public health and increase development costs to industry in order to meet the individual requirements of each region. The divergent recommendations given may result in duplicating non-clinical and/or clinical studies leading to inefficient use of resources. In addition, the evaluation of the potential impact and consequences of the shedding observations (e.g., human-to-human transmission) is complicated by the absence of harmonized recommendations and the high degree of variety in the experimental design of shedding analysis between studies (Schenk-Braat *et al*, 2007[1]), raising an important public health matter.

[1] E.A.M Schenk-Braat *et al*. An inventory of shedding data from clinical gene therapy trials. *JGeneMed* 2007; 9:910-921. (See appendix II)

2. Planning

2.1 What are the main deliverables?

It is proposed that ICH develop a guideline on Virus and Gene Therapy Vector Shedding and Transmission. This ICH guidance would discuss the main principles for the optimisation of analytical methods that are used to characterize and detect shed virus/gene therapy vectors (i.e., sensitivity, specificity, addressing sample interference, and quality of samples) and recommendations for non-clinical, 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. It is expected to:

- harmonize the currently non-aligned guidance noted above;
- facilitate development of products considered to be a global public health need;
- result in refinement and reduction in the use of non-clinical and clinical resources in an area of extensive pharmaceutical research and development;
- close the gaps in available guidance that have become apparent from use of these new therapeutic classes.

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.

2.2 What resources (financial and human) would be required?

An Expert Working Group is proposed to be established. The EWG would include experts from each of the ICH Parties and Observers. The extensive experience of the Gene Therapy Discussion Group (GTDG) in setting out principles for harmonisation (such as general principles to address shedding of virus and vector), would facilitate the development of the proposed guideline. The GTDG includes overall scientific and regulatory expertise in gene therapy medicinal product development (e.g., both gene therapy vectors and oncolytic viruses). It also harbours specific expertise in aspects such as chemistry and manufacturing, non-clinical or clinical oversight of gene therapy medicinal product, knowledge in specific virus shedding patterns (including effects of route of administration), and evaluation of the impact of shedding and transmission on public health and environment. Parties should perhaps consider nominating GTDG members for the proposed EWG due to the aforementioned experience and the already established group dynamics. Additional input to ensure consistency with existing regulatory framework may be needed prior to *Step 2*. It is likely that this EWG will need to liaise with the appropriate (ICH or additional) safety experts to ensure further consistency with non-clinical ICH developments (organisation of joint-meetings, when appropriate).

In addition, the ICH Steering Committee may wish to consider inviting the participation of a representative from one of the major biotechnology associations, and representatives from non-ICH regions involved in gene therapy development and represented in the Global Cooperation Group (such as the Chinese SFDA, etc). EWG members' sponsoring

organisations would need to provide financial resources for periodic face-to-face meetings (twice/year at ICH meetings).

2.3 What is the time-frame of the project?

Three years.

Work will be conducted via teleconferences and email; face-to-face meetings are contemplated twice per year. A 12-month interval is anticipated between the *Step 2* and *Step 4* documents to allow for the usual consultation.

2.4 What will be the key milestones?

The established ICH processes and procedures should be followed. It is expected that the work of the EWG will be completed within this general schedule:

- *Step 2* guideline: Spring 2011;
- *Step 4* guideline: Spring 2012.

3. The impact of the project

3.1 What are the likely benefits (social, health and financial) to our key stakeholders of the fulfilment of the project?

The main benefit will be the production of a single global guidance and prevent the unnecessary duplication of studies to satisfy the requirements related to virus and vector shedding in each region. An ICH consensus effort would avoid any adverse impact to the global development of oncolytic viruses and gene therapy products. This guidance would facilitate global development, and access to needed medicines for patients and avoid wasteful use of valuable resources (including animals). By addressing the specific needs for these classes of therapeutics, e.g., oncolytic viruses and gene therapy products, it should contribute to preventing undue risks to the safety of patients or third parties exposed to such drugs, and contribute to minimizing the likelihood of transmission.

3.2 What are the regulatory implications of the proposed work- is the topic feasible (implementable) from a regulatory standpoint?

Applicable regulations and guidelines in the various regions would be enhanced and clarified by guidance in this area. It should be noted that the need for further guidance has been identified while preparing the ICH considerations on virus and vector shedding (June 2009), which addresses general principles.

4. Post-hoc evaluation

4.1 How and when will the results of the work be evaluated?

The results will be evaluated by the implementation of local requirements in line with this final guideline. A comparison of resources required under current guidance's versus those needed under the new guideline. An assessment is proposed to be made documenting the impact of the guideline in reducing duplication of non-clinical/clinical shedding studies, when performed. A survey of the experience gathered is proposed to be reported to the ICH SC within three years from the formal implementation of the planned ICH guideline.