Considerations from the Gene Therapy Discussion Group meeting
June 10, 2004
(Revised in February 2005*)

The scope of the meeting included an update on new gene therapy developments in the regions and an exchange of information on the main topics agreed upon during the 2003 meeting of the ICH GT discussion group (GTDG). The group also discussed organisational matters relevant to future activities in 2005 and 2006. Representatives from the three ICH regions (including experts from regulatory authorities and industry), Health Canada and EFTA participated.

Update on SCID gene therapy

Updates on the experience in the regions were provided.
Some documented clinical benefits are now available, such as those seen in the X1-SCID and ADA/SCID clinical trials. Encouraging preliminary results are being generated in clinical trials in Graft Versus Host Disease (GVHD) as well.

The group discussed and agreed on general risk factors:

- Subject age
- Copy number/integration events per cell >1 (on average)
- Dose (total number of transduced cells)
- Relative risk associated with transduced cell populations (most to least):
  - –Stem cells with expected selective advantage
  - –Stem cells
  - –T cells or other differentiated cells

New technologies to assess the risks of insertional oncogenesis are being developed and appear to be useful for clinical research purposes but have not yet been validated.
LAM PCR is widely used but since it is not yet validated the use of more than one test could be called for. Dominant bands vary during the disease and do not provide the basis for therapeutic decision-making. If cell clonality trend is detected with a combination of reliable traditional methods, patients should be monitored more often.

The GTDG considered scientifically justified using a combination of methods to improve surveillance for cell clonality as a tool of clinical management. The group also considered valuable the sample archiving for further scientific purposes, as new methods are still in development.

Long-term follow-up (LTFU) of participants in gene therapy clinical trials

FDA presented their current recommendations and background on long-term follow-up of participants in GT clinical trials. All GT trials should have a plan for LTFU for up to 15 years. Data collection should include

De novo cancer
Neurologic disorders*
Rheumatologic disorders
Immunological/haematological disorders

* **Considerations** : In order to avoid confusion with the M2 ESTRI Recommendations that follow the step-wise ICH process, the ICH Steering Committee requested that the outcome of GTDG discussions should now be called "Considerations", rather than "Recommendations".

Physical examinations should be carried out for the first 5 years, followed by a questionnaire for the years 6 to 15 (questionnaire should be kept simple)

This observational information should be collected and submitted annually with the purpose of assessing long term risks for patients involved in GT clinical trials.

The group considers that GT LTFU should be included in the ICH GTDG program in view of the specific features of Gene Therapy that would complement ICH E1 and other Pharmacovigilance documents under development.

HIV vaccination in healthy volunteers: possible risks

The GTDG discussed a number of issues related to the exposure of healthy volunteers to HIV vaccines based on gene therapy products:

- Potential risks related to the manufacturing strategy of vaccinia-derived vectors (e.g., production in primary chicken embryo fibroblasts which could be a source of retroviral sequences)
- Production in non-diploid cell lines of a number of gene therapy vectors used therapeutically or in a preventive mode
- Risks posed by functional HIV genes included in the vector (such as *env*, *nef*, *tat*)
- Long-term monitoring of healthy volunteers
- Risk-benefit balance for healthy volunteers

In the USA, gene-based vaccines used as preventive medicines are not regulated as gene therapy products. In Japan, such vaccines are not regulated as gene therapy products. In the EU, gene-based vaccines are considered to be gene therapy products as defined by Annex I to Directive 2001/83/EC as amended by Directive 2003/63/EC; the EU therefore will continue to explore these aspects and will report to the GTDG on matters which might be relevant.

Replication competent adenovirus (RCA) in replication deficient adenoviral vectors

The level of RCA depends on the production strategy and the particular cells lines used. The amount detected is higher in batches produced in conventional cell lines (e.g., 293 cells) compared to that found in batches produced in recently engineered cell lines (e.g., PER.C6 cells).

PhRMA presented data obtained in conjunction with the administration of high doses of replication deficient adenovirus vectors containing high quantities of RCA

- No serious adverse events related to the RCA were observed using various routes of administration (intratumoral, intrahepatic, intraperitoneal) in cancer patients.
- With respect to environmental risk the presented data suggest that shedding of RCA has not been detected by PCR, which is the most sensitive currently available assay.

EU requires replication deficient adenoviral vectors containing a specified level of RCA to be demonstrated in pre-clinical and clinical studies as safe; at present EU does not recommend specific limits, although generally reduction of RCA presence in

vector lots is recommended. The current FDA recommendation is <1 RCA in $3x10^{10}$ virus particles. Japan evaluates the risks associated with the level of RCA on a case-by-case basis and refers to the FDA recommendations. Health Canada reported that most sponsors have submitted data showing no shedding. Currently Health Canada refers to the FDA RCA limit for their evaluations, but allows some exceptions if not all batches meet the limit.

Consensus was reached that the ICH regions are discouraging high levels of RCA in adenoviral vector batches.

Germline transmission studies

EU presented the discussion held at the CHMP Gene Therapy Expert Group (GTEG) meetings with the goal of developing an addendum to the current GT guideline to assist sponsors and member states. The GTEG wrote a scientific report on a risk assessment approach taking into account a number of factors such as:

- persistence of vector DNA presence
- association with germline cells or other cells (stromal, leukocytes)
- chromosomal integration in germline cells

EU submissions are expected to provide pre-clinical data to show no evidence for risk of inadvertent germline transmission via bio-distribution studies, using good analytical methods.

The regions agreed that bio-distribution studies are important and should be submitted as a part of the clinical development package. The timing for submitting such studies varies by region.

The GTDG considered that it is necessary to continue the discussion with the aim of identifying common principles to minimize the risk of germline transmission.

Future Activities

The next ICH Gene Therapy public workshop will be held in conjunction with the ICH meeting in fall 2005 in USA.
The objectives of the workshops will be to acquire information on the approaches currently being developed with Oncolytic viruses. Issues relevant both to the development of the field and public health will be identified and discussed. The workshop may cover emerging issues including models to study selectivity, attenuation modes, shedding, clinical safety.
The program of the workshop will be further elaborated at the next meeting of the GTDG scheduled to take place in spring 2005.