

**Final Concept Paper**  
**S9: Preclinical Guideline on Oncology Therapeutic Development**  
**30 April 2007**  
*Endorsed by the Steering Committee on 10 May 2007*

**Type of Harmonization Action Proposed**

A harmonised preclinical Oncology guideline is to be published through the ICH process.

**Statement of the Perceived Problem**

The approaches to the preclinical development of oncology drug products have been and continue to be independently discussed and developed in Europe, the USA and Japan. The preclinical approaches are not agreed on across product classes, between small molecules of different molecular mechanisms and across product classes such as biologics and drugs. The available disharmonized guidance has resulted in inefficient use of animal resources, and ineffective drug development in a critical area of human health.

The European Medicines Evaluation Agency (EMA) has official preclinical guidance for the development of cytotoxic cancer treatments. While cytotoxic agents constitute a decreasing class of agents in development, guidance is needed to address the newer, non-cytotoxic (signaling pathways) and context dependent (tumor mutation specific) mechanisms for treatment of cancer now in development. Nor are biologic approaches that include both cytotoxic and non-cytotoxic mechanism addressed in these guidances. The FDA is developing guidances for biologic therapeutics and drugs that will broadly address preclinical development of the various mechanisms of cancer therapy. Further, in the context of FDA's Exploratory IND Guidance, some preclinical approaches to early investigative oncology drug development are briefly outlined, although not limited to this therapeutic application. The MHLW is currently developing preclinical guidance that will address various mechanisms of anticancer therapy, but will not include biologics in its scope. Thus, there is substantial concern that, when these guidances are completed, they will not offer a harmonized approach for preclinical development of drugs needed for the treatment of cancer.

This independent proliferation of guidances focused on preclinical issues in oncology drug development highlights the critical need for guidance on this topic and indicates the inadequacy of the current state. While these current independent approaches have their merits, the dissociated efforts will likely result in disparate recommendations that will adversely impact global development of needed cancer therapies. The result will be both delays in the availability of needed agents and waste of valuable resources, including test animals.

Amplifying this problem, is the fact that most ICH S guidances and M3 either explicitly or implicitly exclude cancer therapies from their recommendations, yet there is no alternative offered for a harmonized product development strategy. As a result, M3 or S6 guidance is often inappropriately relied on (or expected) particularly for non-cytotoxic and biologic agents in development of cancer therapeutics.

An ICH guidance that focuses on preclinical recommendations to support the development and marketing of cancer therapeutic agents for the treatment of primary cancer, would:

- 1) address the current state of disharmony noted above;
- 2) facilitate development of agents meeting a global critical public health need;
- 3) result in refinement and a relevant reduction in the use of experimental animals in an area of extensive drug research and development; and
- 4) address the gaps in preclinical development guidance that have arisen from the new therapeutic classes of targets identified from the human genome project, and recent advances in cancer biology.

### **Issues to be Resolved**

- 1) Scope of the guidance: Therapeutic classes to be included; Preclinical development approach in relation to product class and how to cover the breadth of the product classes in the oncology guidance; classes to be excluded are therapeutic vaccines, cell and gene therapy.
- 2) Necessity for long term preclinical testing to support early clinical trials
- 3) Duration, species, type of non-clinical safety studies to support the early and late development phases
- 4) Harmonization of approaches to the extent justified for biological and small molecules

### **Type of Expert Working Group**

We recommend setting up an Expert Working Group (EWG) which includes representatives/experts of the six ICH parties and observers on request.

### **Timetable**

The EWG should be summoned to the ICH meeting in Yokohama in October 2007 to draw up a step 1 document. Existing draft MHLW and FDA Guidances as well as existing EMEA guidances should be consulted as an initial framework. Subsequently, the EWG is to be asked to release a step 2 document by October 2008 and a step 3 document by June 2009. A step 4 document should be completed by early 2010. This aggressive time line could be anticipated based on the advanced work that is currently being undertaken on guidance development by MHLW and FDA.

### **Parties Making the Proposal**

PhRMA proposed this issue as a new Safety topic for ICH at the October 2006 meeting. All parties supported the development of an Oncology guidance.