

Final Concept Paper
M3(R2): Revision of ICH M3(R1):
Maintenance of the ICH Guideline on Non-Clinical Safety Studies
for the Conduct of Human Clinical Trials for Pharmaceuticals
dated 9 September 2006
Endorsed by the Steering Committee on 20 September 2006

Type of Harmonisation Action Proposed

A revision of the existing tripartite guideline ICH M3 – *Nonclinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals* is proposed as a result of the discussions held during the Safety Brainstorm meeting in June 2006.

The revision of the guideline is justified by the existence of new data and of new approaches for nonclinical and clinical research as compared to those covered in the ICH-M3 guideline.

A positive impact on public health associated to the acceleration of the drug development process allowing for an earlier access to innovative drugs is anticipated.

An overall reduction of animals use and suffering is expected as a consequence of the alteration and harmonization of the nature of the nonclinical study package as proposed.

Statement of the Perceived Problem:

The approved text of the existing ICH-M3 guideline include significant regional differences needing to be revisited in light of accumulated information. Such differences include different aspects related to the timing and or nature and duration of studies eg reproductive toxicity or repeated dose toxicity to support the conduct of different phases of clinical trials. Moreover, the requirement of the toxicity package to support phase I clinical trials does not take into consideration emerging approaches for first administration in man eg *Exploratory IND Studies* including *Clinical Trials with a Single Microdose* for which new FDA and CHMP guidance have been released and/or are in preparation, with some level of disharmony.

Issues to be Resolved:

The issues to be discussed in the revision process include:

- The timing of completion of the genotoxicity core battery.
- Nature and timing of reproductive toxicity studies to support the conduct of different phases of clinical trials.
- The duration of repeated dose toxicity studies to support the conduct of different phases of clinical trials.
- The duration of chronic toxicity studies in non-rodents.
- The requirement of the toxicity package to support first entry into human.
- The need to keep single dose toxicity studies as a fixed requirement prior to first human exposure.
- Defining the role of M3 guideline in the development of biotechnology derived pharmaceuticals.

Background to the Proposal:

For inclusion of women of childbearing potential (WCBP) in clinical trials, in the EU assessment of embryo-fetal development should be completed prior to Phase I trials and female fertility

studies prior to Phase III clinical trials. In the US, the inclusion of WCBP is allowed in carefully monitored studies without reproductive toxicity studies provided appropriate precautions are taken to minimise the risk (birth control and informed consent).

In Japan, assessment of female fertility and embryo-fetal development should be completed prior to the inclusion of women of childbearing potential using birth control in any type of clinical trial. Former Japanese disagreement was based on two reasons. One was on the unreliability of clinical management for contraception; however, because of social changes in awareness of clinical management for this issue, it may be decided more flexible. Another difficulty was in the issue that a two-week-testing was considered to be inadequate to obtain a confident fertility data. If this could be answered, Japanese opinions may be changed.

- The current M3 guideline states that “the single dose (acute) toxicity for a pharmaceutical should be evaluated in two mammalian species prior to the first human exposure.” The extent of utility and timing of such studies in assessing human safety could be evaluated and could potentially result in a significant decrease in animal use and suffering.
- The duration of repeated dose toxicity studies to support the conduct of different phases of clinical trials are different in the EU as compared to US and Japan, as illustrated in the Table below:

Duration of Repeated Dose Toxicity Studies to Support Phase I and II Trials in the EU and Phase I, II, and III Trials in the United States and Japan¹

Duration of Clinical Trials	Minimum Duration of Repeated Dose Toxicity Studies	
	Rodents	Nonrodents
Single Dose	2-4 Weeks ²	2 Weeks
Up to 2 Weeks	2-4 Weeks ²	2 Weeks
Up to 1 Month	1 Month	1 Month
Up to 3 Months	3 Months	3 Months
Up to 6 Months	6 Months	6 Months ³
> 6 Months	6 Months	Chronic ³

¹ In Japan, if there are no Phase II clinical trials of equivalent duration to the planned Phase III trials, conduct of longer duration toxicity studies should be considered.

² In the EU and the United States, 2-week studies are the minimum duration. In Japan, 2-week nonrodent and 4-week rodent studies are needed. In the United States, as an alternative to 2-week studies, single dose toxicity studies with extended examinations can support single dose human trials.

³ Data from 6 months of administration in nonrodents should be available before the initiation of clinical trials longer than 3 months. Alternatively, if applicable, data from a 9-month nonrodent study should be available before the treatment duration exceeds that which is supported by the available toxicity studies.

- In addition, 12 Months chronic toxicity studies in non-rodents are being conducted in response to perceived requirements of some Regulatory Authorities, while for other Authorities 6 or 9 months non-rodent studies are acceptable.
- Innovative approaches for first entry into human clinical trials currently being adopted by Industry with screening purposes are not appropriately considered in the existing guideline. A tailored package of supportive nonclinical studies is recommended by FDA [*Exploratory IND Guidance*] and the EU [*Clinical Trials with a Single Microdose*] and additional proposals are still under discussion. Articulation of these regulatory documents is highly desirable. Japanese parties have no official concept on this area but consider that it would be highly useful not only for Japanese pharmaceuticals but also for government.

References:

FDA Guidance to Industry, Investigators, and Reviewers: Exploratory IND Studies, January 2006;

CHMP Position Paper on Nonclinical safety Studies to support Clinical trials with a single microdose, June 2004.

Concept paper....low dose clinical trials

ICH Guidance for Industry: M3 Nonclinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals

Type of Expert Working Group: The EWG should be a six-party group.