



ICH M3 (R2) —Guideline on Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals

International Conference on Harmonisation of Technical
Requirements for Registration of Pharmaceuticals for Human Use



Background

- Major revisions to ICHM3(R1) were begun in 2006
- ICHM3(R1) had only a few minor editorial changes to the original ICHM3
- ICHM3(R1) had a number of areas for which harmonization had not been fully achieved in original guidance (ICHM3) more than 10 years ago
- Consideration of recent regulatory documents was desirable
- Step 2 reached in June 2008

Objectives of ICHM3

- **To recommend international standards for, and promote harmonisation of, the nonclinical safety studies to support human clinical trials of a given scope and duration, and for the marketing authorization of drug products**

Scope of Revisions to ICHM3(R1) (a)

- Acute toxicity studies
- Limit dose in toxicity studies
- Duration of repeat dose studies for non-rodents
- Estimation of the first dose in human
- Exploratory clinical studies: limited clinical studies with nonclinical testing program directed only to support those early exploratory approaches
- Genotoxicity studies

Scope of Revisions to ICHM3(R1) (b)

- **Reproduction toxicity studies**
- **Timing for special studies**
 - **Toxicity studies to support clinical trials in Pediatric population**
 - **Immunotoxicity studies**
 - **Phototoxicity studies**
 - **Nonclinical Abuse liability studies**
 - **Fixed Combination drug non-clinical studies**

Acute Toxicity Studies

- Stand alone studies rarely needed
- Short-term, dose-limiting toxicity can be learned from repeat-dose studies
- Information on the short-term dose-limiting toxicity of pharmaceuticals should be available prior to Phase 3

Limit Dose for General Toxicity Studies

- **Dose limit- 1000 mg/kg/day for rodents and non-rodents if the human dose does not exceed 1 g per day and there are 10x margins to clinical exposure**
- OR**
- **Exposure margin limit- Only need to go to 50x the maximum human exposure at the anticipated max recommended human dose**
 - **In U.S. if dose-limiting toxicity has not been identified, 1 study of at least 1 month recommended before phase 3 study at MFD or MTD, whichever is lower**

Duration of Repeated Dose Toxicity Studies in Non-rodents

- Reviewed data for all accumulated data sets (dogs, primarily) for about 150 compounds developed for diverse indications from EU countries, the U.S., and Japan--1999-2006
- Re-evaluated 6 vs 9 vs 12 months for opportunity to minimize exceptions to 9 month's duration

Duration of Repeated Dose Studies in Non-rodents

- **Criterion: Would clinical decisions have changed based on new toxicity uncovered in longer term studies?**
- **6 months in non-rodents (primarily dogs) is usually but not always sufficient**
- **No data that show that 9 months is not sufficient**
- **9 month non-rodent chronic studies should be adequate to support chronic use in human (small molecules) without exception**

Exploratory Clinical Studies (a)

- **5 exploratory clinical studies approaches (no therapeutic or diagnostic intent, MTD not examined) are described as examples.**
- **Supportive non-clinical programs are focused on direct support of those early clinical studies with limited clinical objectives, not on further development**

Five Exploratory Clinical Studies (b)

- **Two microdose approaches**
 - Total dose of 100 µg
 - Up to 5 administration of a maximum of 100 µg/administration
- **Single dose subtherapeutic studies**
- **Two Repeated dose exploratory studies:**
 - Exposure based (overage approach)
 - Duration of clinical trial up to duration of dosing in non rodent toxicity studies; an alternate path

Microdose Approach- 1

- Total dose of 100 µg, max of 5 administrations and 1/100th NOAEL and 1/100th Pharmacologically active dose, scaled
- Extended single dose tox study in 1 species by intended route and PK; max dose of 1000x clinical dose, scaled
- PD profile in vitro and in relevant model; genetox not needed

Microdose Approach- 2

- Total dose of 500 µg, 100 µg per dose, max of 5 administrations, with washout between and 1/100th NOAEL and 1/100th Pharmacologically active dose, scaled
- 7-d repeat dose tox study in 1 species by intended route and PK; max dose of 1000x clinical dose, scaled
- PD profile in vitro and in relevant model; genetox not needed

3. Single Dose Subtherapeutic Clinical Studies

- **Starting clinical dose depends on toxicity in extended single dose toxicity studies in rodents and nonrodents in which top dose was MTD, MFD, or limit dose**
- **Max clinical dose: $\frac{1}{2}$ the NOAEL exposure in the more sensitive species, if tox is monitorable and reversible**
- **nonclin safety pharm; Ames assay**

4. Single or Repeated Dose Clinical Studies into Therapeutic Range but Not to Evaluate MTD, Exposure Based (a)

- **Starting Dose: If tox in both species: follow regional guidance for the starting dose**
- **Without any tox in either species or tox in one species, starting clinical dose should not exceed 1/50 the NOAEL in the more sensitive species (mg/m²); for other considerations, follow regional guidance**

4. Single or Repeated Dose Clinical Studies into Therapeutic Range but Not to Evaluate MTD, Exposure Based (b)

- **Max Clin dose:**
- **With tox in both species, max clin dose based on std risk assessment but typically would not exceed the lowest NOAEL AUC**
- **Without tox in both species, clin dosing up to 1/10 the lower exposure (AUC) in either species at highest dose tested**
- **If tox in one species, max clin dose would be whatever gave the lower exposure of the above 2 options**

4. Single or Repeated Dose Clinical Studies into Therapeutic Range but Not to Evaluate MTD, Exposure Based (c)

- **Std 2-wk repeat dose toxicity studies in rodent and nonrodents, with dose selection in animals based on multiples of the anticipated clinical AUC at the max dose**
- **Nonclin safety pharm; Ames assay**

5. Single or Repeated Dose Clinical Studies into Therapeutic Range but Not to Evaluate MTD (linked to duration) (a)

- **Starting clinical dose should not exceed 1/50 the NOAEL in the more sensitive species(mg/m²)**
- **Max clinical dose: not higher than the AUC at the NOAEL exposure in the nonrodents or 1/2 AUC at the NOAEL in the rodent species, whatever is lower (up to 14 days)**

5. Single or Repeated Dose Clinical Studies into Therapeutic Range but Not to Evaluate MTD (linked to duration) (b)

- **Std 2-wk repeat dose toxicity studies in rodent (with justification for rodent) and, confirmatory study in nonrodent with duration of a minimum of 3 days and up to clinical study duration**
- **Nonclin safety pharm**

Genotoxicity Studies

- A gene mutation assay is sufficient to support all single dose clinical development trials
- For multiple dose clinical development trials, choice of two batteries of tests, Option 1 and Option 2: described in the ICH S2R document

Reproduction Toxicity Studies (a)

- Nature and timing of reproductive toxicity studies to support the conduct of different phases of clinical trials
- Reviewed data sets from dose ranging and definitive studies in rats and rabbits (several hundred drugs developed for diverse indications from EU countries, the U.S., and Japan--1999-2006
- Criterion: How well do dose-ranging studies predict those results of definitive studies that would changed clinical decisions or have an impact on labeling.

Reproduction Toxicity Studies (b)

- When dose-ranging studies are available and visceral/skeletal examinations are conducted—good predictivity
- WOCBP (up to 150) with control of pregnancy risk could receive investigational treatment for up to 3 months before completion of definitive reproductive toxicity studies
- WOCBP= women of child-bearing potential

Reproduction Toxicity Studies (c)

- **FDA allows such clinical trials without dose-ranging studies**
- **In the EU and Japan, although definitive studies are generally required to support inclusion of WOCBP in clinical studies, some situations are defined where early clinical studies could be conducted in WOCBP before completing embryo-fetal developmental studies in animals. These include short duration clinical trials (such as 2 weeks) with intensive control of pregnancy risk.**

Timing for Special Studies

- **Toxicity studies to support clinical trials in Pediatric population**
- **Immunotoxicity studies**
- **Phototoxicity studies**
- **Nonclinical Abuse liability studies**
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3Rs Achievements (a)

Overall harmonization will result in reduction and refinement of animal use:

- **Separate acute toxicity studies were eliminated. (reduction)**
- **Repeated dose toxicity studies now have exposure and dose limits to establish valid study designs. (refinement and reduction of the need to repeat studies)**

3Rs Achievements (b)

- **New exploratory clinical studies section will reduce use of animals needed to support clinical studies and offer refinement of toxicology study design. (reduction and refinement)**
- **Local tolerance toxicity: recommended against stand alone designs. (reduction)**
- **Reproductive toxicity studies are deferred until later in development and this will result in elimination of studies for failed compounds. (reduction)**

3Rs Achievements (c)

- **Pediatric recommendations will eliminate routine use of second juvenile toxicity study and minimize when juvenile toxicity studies are needed. (reduction)**
- **Recommended that photocarcinogenicity studies generally are not of value for pharmaceutical development. (reduction)**
- **Abuse liability: generally recommended against use of primates with preference for rodent with limited doses. (reduction and refinement)**
- **Studies of combination drugs recommended to be limited to 1 species, usually rodent**

ICH M3 (R2) Current Status

- Signed off on step 2 in July 2008
- Started discussing public and 6-party comments on a number of the revisions in November 2008 in Brussels
- Had 3 webex meetings in January 2009
- Had an interim Meeting in MD in the U.S. in March 2009 and finished addressing all comments received on the step 2 document

Issues to be Discussed in Yokohama 2009 (a)

- **Will evaluate data from JPMA, EFPIA, and PhRMA on need for skeletal evaluation in dose ranging embryofetal development study used to support studies in women up to 150 for up to 3 months**
- **S2R needs to be final for M3 to be final, so it can be referred to in ICHM3R2**

Issues to be Discussed in Yokohama 2009 (b)

- **Concurrence between S6 addendum and M3 has to be assured regarding timing for embryofetal/development/ peripostnatal studies for mAb in NHP**
- **Address any further comments on revisions to step 2 document as revised thus far**
- **Finish reading through the entire document**



Outcomes of the Yokohama Meeting



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Conclusions

- This revision R2 of ICH M3 which includes further harmonisation for non-clinical safety studies will help to define current recommendations and reduce the likelihood that substantial differences will exist between regions
 - ICHM3(R2) should facilitate timely conduct of clinical trials and reduce the unnecessary use of animals and other resources
 - This should promote safe and ethical development and availability of new pharmaceuticals
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