

Summary of ICH Safety Topics Oct 2008

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



Topics

- **ICHM3R2 Abby Jacobs**
- **ICHS6 Anne Pilaro**
- **ICHS2R David Jacobson-Kram**
- **ICHS9 John Leighton**

ICHM3: Guideline on Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals

- **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**

Scope of Revisions to ICHM3(R1) (a)

- **Acute toxicity studies**
- **Limit dose in toxicity studies**
- **Duration of repeat dose studies for non-rodents**
- **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
- **Considerable progress in harmonization**

Acute Toxicity Studies

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

Limit Dose for General Toxicity Studies

- Dose limit- 2000 mg/kg/day for rodents and 1000 mg/kg/day for non-rodents if the human dose does not exceed 1 g per day and there are significant 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
- Details still under discussion

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 – which the FDA supports-allows more clinically than the older FDA guidance, so somewhat more is needed nonclinically;**
 - **Total dose of 100 µg in humans**
 - **Up to 5 administrations of a maximum of 100 µg/administration in humans**
- **Single dose sub-therapeutic studies**
- **Two Repeated dose exploratory studies:**
 - **Exposure based (overage approach)**
 - **Duration of clinical trial up to duration of dosing in non rodent toxicity studies**

Genotoxicity Studies

- **A tiered approach**
- **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**

M3 Guidance for Genotoxicity (a)

- **A Gene mutation assay is sufficient to support all single dose clinical development trials**
- **For multiple dose clinical development trials, Option 2, if selected, to be completed before first human use in multiple dose studies.**

M3 Guidance for Genotoxicity (b)

- ***In vitro* components of Option 1, if selected, to be completed before first multiple dose human studies**
- **The *in vivo* component of Option 1 to be completed prior to Phase 2**
- **If a positive finding occurs, assessment, and possibly additional testing to be conducted to determine if further administration to human is still appropriate**

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
- WOCCBP (up to 150) with control of pregnancy risk could receive investigational treatment for up to 3 months before completion of definitive reproductive toxicity studies
- WOCCBP= 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**
 - The 3T3 assay has resulted in many false positives, so not mentioned
- **Nonclinical Abuse liability studies**
- **Fixed Combination drug non-clinical studies**

ICH S6

- **The Biologics Guidance**

S6 Discussion (1)

- **Do we need an update of the ICH S6 guideline?**
- **Yes. All parties agreed that there is a need for further specification under the condition that the case-by-case approach of the existing guidance document should be maintained.**

S6 Discussion (2)

- **What should be the form of updating?**
 - Addendum
 - Questions and Answers
 - Revisions incorporated in the present text
- **Pros and cons?**
 - Need for public consultation
 - Need for revision of the guidance
 - Duration of the process different?
 - Number of topics and details of those
 - Complexity and interrelationship

S6 Discussion (3)

- **What topics do we need to update?**
 - **5 topics**
 - **Species Selection**
 - **Study design**
 - **Reproductive/developmental toxicity**
 - **Carcinogenicity**
 - **Immunogenicity**
- **With these topics the group agreed to work on an addendum to S6**

S6 Topic for clarification 1

■ Species Selection

- How to justify the choice of a species
- Clarify role of tissue cross-reactivity
- When to use a second species?
- Use of alternative models
 - Use of transgenics
 - Use of homologues

S6 Topic for clarification 2

- **Study design issues**
 - **Scientific justification of duration**
 - **High dose selection**
 - **Utility and length of recovery**

S6 Topic for amplication and clarification 3

- **Reproductive/Developmental toxicity studies**
 - **Justification of species selection**
 - Rodents/non-rodents
 - transgenics/homologues
 - **Considerations when using primates**
 - Use of combined study designs in monkeys. Timing.
 - How to get data on fertility
 - Impact of placental transfer
 - How to get data from the F1 generation?

S6 Topic for clarification 4

■ Carcinogenicity

- Justification for the approach to address carcinogenic risk
- Application of in vivo models
 - Length of the studies
 - Use of proliferation indices
 - Use of homologues

S6Topic for amplification and clarification 5

■ Immunogenicity

- Extent of characterization**
- Impact of neutralizing vs. non-neutralizing.**
- Role of PD markers**
- Assessment in recovery groups**

S6 Way Forward

- **Expert Working Group to meet in Brussels (10-13 November 2008)**
 - **Start in November 2008 with discussion on various topics, presenting the background data**
 - **Writing the addendum in June/November 2009: Step 2**
 - **Consultation period: 6 months**
 - **Step 4 in June 2010**

S2R Guidance for Genotoxicity

- Reached step 2 in 2007
- Discussed comments to the docket in Portland June 2008
- Not meeting Brussels in Oct 2008
 - Conducting laboratory work to see whether in vivo comet assay can be incorporated into the repeat dose toxicology study

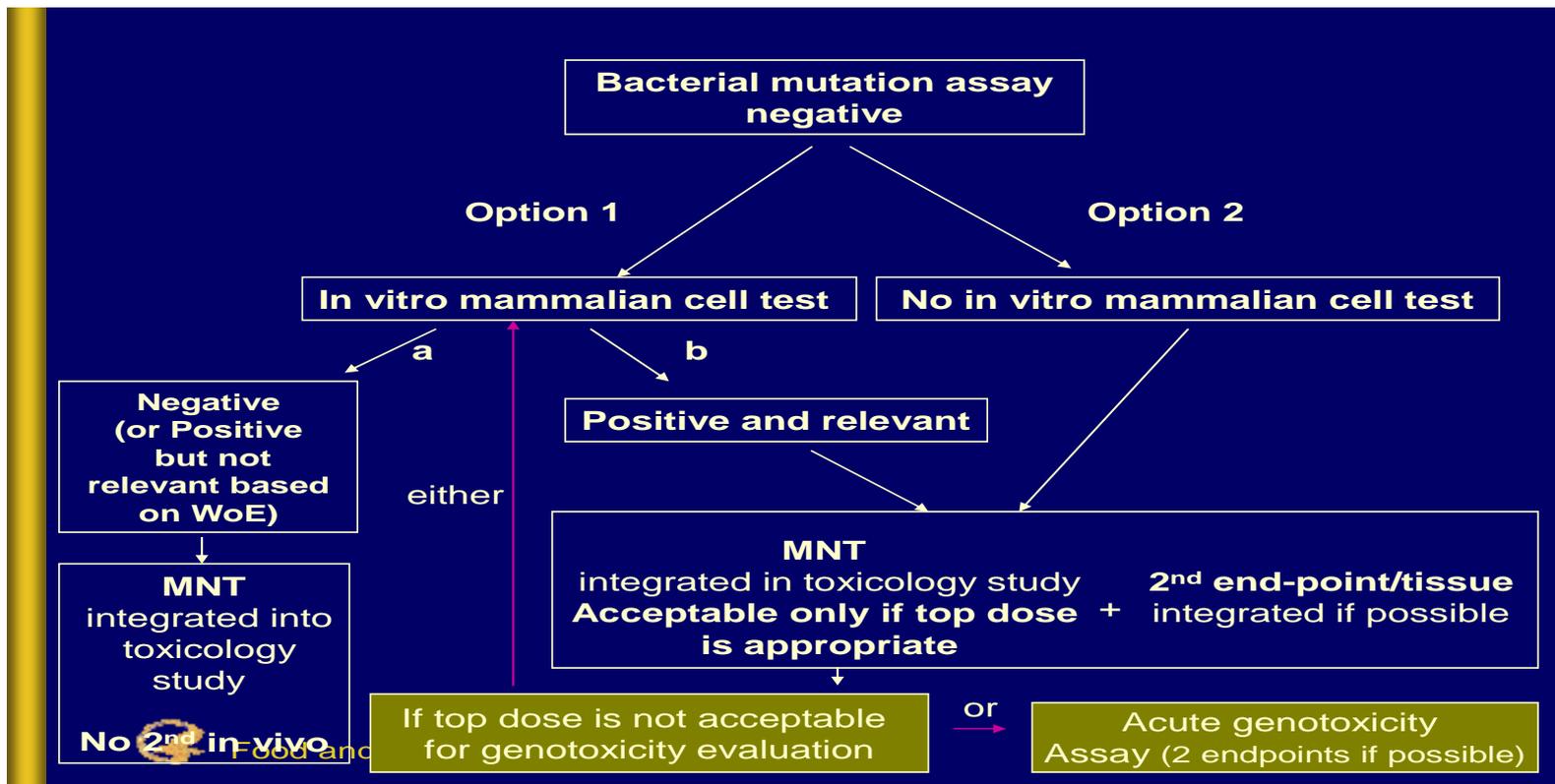
S2R Guidance for Genotoxicity-option 1

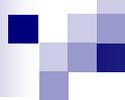
- A test for gene mutation in bacteria
- A cytogenetic test for chromosomal damage (*in vitro* metaphase chromosome aberration test or *in vitro* MN test), or an *in vitro* mouse lymphoma *tk* gene mutation assay
- An *in vivo* test for genotoxicity, generally a test for chromosomal damage using rodent hematopoietic cells, either for micronuclei or for chromosomal aberrations in metaphase cells

S2R Guidance for Genotoxicity-option 2

- **A test for gene mutation in bacteria**
- **An *in vivo* assessment of genotoxicity with two tissues, usually an assay for micronuclei using rodent hematopoietic cells and a second *in vivo* assay**

Genotox Summary





S9 Guidance for Oncology

- **Nonclinical Recommendations for the Development of Anticancer Drugs and Biologicals**

ICH S9- history

- **Business plan proposed by PhRMA**
- **Endorsed by ICH Steering Committee May 2007**
 - **Separate regional oncology guidances were in development**
 - **ICH M3 and S6 were being used outside of US and are not appropriate for development of anticancer drugs**
- **Expert Working Group formed summer 2007**
- **First meeting Yokohama Japan Oct 2007**
 - **Japan, EU, and US discussed current and proposed approaches to anticancer drug and biological development**
- **Additional meetings Portland OR (June 2008) and Brussels (Nov 2008)**
- **Milestones:Planned release:Step 2: October 2008;Step 4: Early 2010**

Update Status Post Portland

■ FDA

- Circulated Portland S9 draft guidance
- Aug 4, 2008 presentation internally to CDER/CBER oncology group
- General agreement on topics

■ EU, MHLW

- Obtained feedback from colleagues Sept
 - Shared report with EWG
 - Reported general agreement on many topics
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S9: Issues Discussed in Portland

- **Need to clearly identify differences between**
 - Oncology drugs and other indications
 - Drugs and biologic
- **Major topics:**
 - Approaches to setting the first in human start dose
 - Duration and timing of chronic toxicology studies
 - Need for reproductive toxicology studies
- **Cross reference to other guidance where relevant to reduce maintenance of S9**
- **Importance of 3R's**

S9: Issues to Discuss

- Approach to start dose
 - Agreed on need to administer pharmacologically active dose but one that is reasonably safe
 - Maximal start dose could be based on:
 - All available data (EU specified this approach)
 - Pharmacology
 - Toxicology – allows for maximum start dose
 - Multiple approaches acceptable but must be justified
 - 1/10th a severely toxic dose to 10% of the animals
 - 1/6th the highest non severely toxic dose
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S9: Issues to Discuss

- **Duration and timing of toxicology studies for drugs**
 - **Current approach is to provide 6 month studies with NDA**
 - **FDA proposed 3 month studies to be submitted prior to phase 3; general agreement**
 - **Similar approach for biologics?**

S9: Issues to Discuss

■ Reproductive toxicology

- Currently embryo-fetal study is to be provided with NDA
- Discussion
 - Are separate fertility studies needed?
 - Data to be collected as part of repeat dose general toxicology studies
 - Full evaluation may be needed in some patient populations, e.g., when a therapy is essentially curative
 - EU suggests fertility studies needed in all cases

S9: Issues to Discuss

■ Discussion:

- Embryo-fetal and peri- and postnatal evaluation to be conducted
 - Exception: “cytotoxic” drugs

- Timing of reproductive studies
 - Embryo-fetal and peri- and postnatal studies:
 - Need to provide at
 - NDA?
 - Prior to phase 3? No clarification yet from EU