IND-Enabling Safety Studies for Rare Diseases

Timothy J. McGovern, Ph.D.
ODE II Associate Director for Pharmacology/Toxicology
September 16, 2014
Disclaimer

This speech reflects the views of the speaker and should not be construed to represent FDA’s views or policies.
Overview

- Nonclinical considerations for development of products for rare diseases
- Nonclinical considerations for ERTs (enzyme replacement therapies)
- Summary of toxicity data from a survey of FDA’s internal database for ERTs
- Future direction of nonclinical requirements for ERTs
- Conclusions
Rare diseases

- In the US, approximately 6800 rare disorders affecting ~ 30 million people

- This classification covers a broad range of disease severities and associated life expectancies

- The nonclinical program expected to support initial clinical trials, ongoing development, and eventual approval is directed by the overall clinical risk:benefit ratio for a given product
Role of nonclinical studies

- Provide evidence that drug is “reasonably safe to conduct the proposed clinical investigation” [21 CFR 312.23(a)(8)]
- Provide understanding of drug’s mechanism of action
- Inform the design of early stage clinical trials (starting dose, dose escalation, dosing regimen, route of administration)
- Guide patient eligibility criteria and safety monitoring procedures
- Identify/predict risks that aren’t readily identified in human trials (eg, carcinogenicity, reproductive toxicity)
Relevant guidance documents for discussion of nonclinical programs

- **ICH M3(R2)** – general guidance for nonclinical drug development
  - Key aspects of IND-enabling program include
    - Pharmacology (in vitro/in vivo)
    - Pharmacokinetics/Toxicokinetics (PK/TK)
    - General toxicology
    - Genetic toxicology

- **ICH S6(R1)** – development issues specific to biologics

- **ICH S9** – development of oncology drugs for “late stage or advanced disease” for small molecules and biologics
“Standard” nonclinical toxicity programs under ICH M3

ICH M3:

Table 1  Recommended Duration of Repeated-Dose Toxicity Studies to Support the Conduct of Clinical Trials

<table>
<thead>
<tr>
<th>Maximum Duration of Clinical Trial</th>
<th>Recommended Minimum Duration of Repeated-Dose Toxicity Studies to Support Clinical Trials</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rodents</td>
</tr>
<tr>
<td>Up to 2 weeks</td>
<td>2 weeks&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Between 2 weeks and 6 months</td>
<td>Same as clinical trial&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>&gt; 6 months</td>
<td>6 months&lt;sup&gt;b, c&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Nonrodents</td>
</tr>
<tr>
<td></td>
<td>2 weeks&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Same as clinical trial&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>9 months&lt;sup&gt;b, c, d&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

ICH S6: Studies in a single relevant animal model can be acceptable.
ICH M3 allows for flexibility in approach

- Nonclinical safety studies and human clinical trials should be planned and designed to represent an approach that is scientifically and ethically appropriate.

- Pharmaceuticals under development for indications in life-threatening or serious diseases (e.g., advanced cancer, resistant human immunodeficiency virus (HIV) infection, and congenital enzyme deficiency disease) without current effective therapy also warrant a case-by-case approach to both toxicological evaluation and clinical development in order to optimize and expedite drug development.

- In these cases and for products using innovative therapeutic modalities ..., particular studies can be abbreviated, deferred, omitted, or added.
Applying flexibility

- Patients and parents of children with rare diseases request increased access to investigational products, sometimes prior to conduct of the minimum nonclinical studies to assess safety.

- Sponsors express desire for greater flexibility at times.

- Many CDER Office of New Drug review divisions apply some flexibility in nonclinical requirements for rare disease products, including those to treat inborn errors of metabolism such as enzyme replacement therapies (ERTs).

- The degree of flexibility for a given program is based on discussions with clinical review team.
What should be the basis for accepting an abbreviated nonclinical toxicology program?

- The precedent, quite reasonably, has been risk versus benefit.

- This paradigm is clearly exemplified in ICH S9.
  - For serious and life threatening disease, higher levels of risk are appropriate.
Comparison of ICH M3(R2) and ICHS9
Comparison of ICH S9 and M3(R2): Studies and Timing - Pharmacology

<table>
<thead>
<tr>
<th>ICH S9</th>
<th>ICH M3(R2)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Studies</strong></td>
<td><strong>Studies</strong></td>
</tr>
<tr>
<td>Safety pharmacology parameters can be incorporated into general toxicology studies</td>
<td>Core battery of safety pharmacology studies (ICH S7A and S7B), usually stand-alone</td>
</tr>
<tr>
<td><strong>Timing</strong></td>
<td><strong>Timing</strong></td>
</tr>
<tr>
<td>Prior to Phase 1</td>
<td>Prior to Phase 1</td>
</tr>
</tbody>
</table>

**Pharmacology**

ICH S9 provides guidance on how safety pharmacology parameters can be incorporated into general toxicology studies, typically prior to Phase 1. ICH M3(R2) requires a core battery of safety pharmacology studies, which are usually stand-alone and also conducted prior to Phase 1.
Comparison of ICH S9 and M3(R2): Studies and Timing - PK/TK

<table>
<thead>
<tr>
<th>ICH S9</th>
<th>ICH M3(R2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Studies</td>
<td>Studies</td>
</tr>
<tr>
<td>Timing</td>
<td>Timing</td>
</tr>
<tr>
<td>ADME*</td>
<td>ADME*</td>
</tr>
<tr>
<td>Concurrent with clinical studies</td>
<td>Generally Prior to Phase 3</td>
</tr>
<tr>
<td>Studies of unique human metabolite</td>
<td>Studies of unique human metabolite</td>
</tr>
<tr>
<td>Not warranted</td>
<td>Prior to Phase 3</td>
</tr>
</tbody>
</table>

*ADME: Absorption, distribution, metabolism, and excretion
## Comparison of ICH S9 and M3(R2): Studies and Timing - General Toxicology – Initiation of clinical trials

<table>
<thead>
<tr>
<th>ICH S9</th>
<th>ICH M3(R2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Studies: 28 day repeat dose toxicology studies (rodent and non-rodent)</td>
<td>Studies: Repeat dose toxicology studies (rodent and non-rodent) similar to duration of clinical trial</td>
</tr>
<tr>
<td>Timing: Support single through continuous clinical dosing (if patient benefits)</td>
<td>Timing: Prior to conducting clinical trials</td>
</tr>
</tbody>
</table>
Comparison of ICH S9 and M3(R2): Studies and Timing - General toxicology – Support of start dose

<table>
<thead>
<tr>
<th>ICH S9</th>
<th>ICH M3(R2)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Studies</strong></td>
<td><strong>Timing</strong></td>
</tr>
<tr>
<td>Identification of NOAEL or NOEL is not essential in 28 day repeat dose toxicology study</td>
<td>NA</td>
</tr>
</tbody>
</table>

NOAEL: No-observed-adverse-effect level
NOEL: No-observed-effect-level
Comparison of ICH S9 and M3(R2): Studies and Timing - General toxicology – Marketing

<table>
<thead>
<tr>
<th>ICH S9</th>
<th>ICH M3(R2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Studies</td>
<td>Timing</td>
</tr>
<tr>
<td>3 month repeat dose toxicity (rodent &amp; non-rodent)</td>
<td>Prior to phase 3; supports marketing</td>
</tr>
</tbody>
</table>
## Comparison of ICH S9 and M3(R2): Studies and Timing - Genetic Toxicology

<table>
<thead>
<tr>
<th></th>
<th>ICH S9</th>
<th>ICH M3(R2)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Studies</strong></td>
<td>Complete battery (if in vitro are +, in vivo may not be needed)</td>
<td>In vitro studies support early clinical trials</td>
</tr>
<tr>
<td><strong>Timing</strong></td>
<td>Marketing</td>
<td>Prior to FIH Phase 1 (Ames) Prior to repeat dose clinical trials (clastogenicity assay)</td>
</tr>
</tbody>
</table>

**ICH S6:** Studies are not applicable.

**FIH:** First in humans
### Comparison of ICH S9 and M3(R2): Studies and Timing - Reproductive Toxicology

<table>
<thead>
<tr>
<th>ICH S9</th>
<th>ICH M3(R2)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Studies</strong></td>
<td><strong>Studies</strong></td>
</tr>
<tr>
<td>EFD study in 2 species (unless rodent is positive)</td>
<td>Fertility studies and EFD studies (2 species)</td>
</tr>
<tr>
<td><strong>Timing</strong></td>
<td><strong>Timing</strong></td>
</tr>
<tr>
<td>Marketing</td>
<td>Prior to Phase 3</td>
</tr>
<tr>
<td></td>
<td>Pre- and post-natal development study</td>
</tr>
<tr>
<td></td>
<td>Marketing</td>
</tr>
</tbody>
</table>

EFD: Embryo-fetal development
Comparison of ICH S9 and M3(R2): Studies and Timing - Carcinogenicity

<table>
<thead>
<tr>
<th>ICH S9</th>
<th>ICH M3(R2)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Studies</strong></td>
<td><strong>Studies</strong></td>
</tr>
<tr>
<td>Not warranted</td>
<td>Assessment in 2 species (if warranted for indication)</td>
</tr>
<tr>
<td><strong>Timing</strong></td>
<td><strong>Timing</strong></td>
</tr>
<tr>
<td>NA</td>
<td>• Marketing</td>
</tr>
<tr>
<td></td>
<td>• Clinical trials if identified cause for concern</td>
</tr>
<tr>
<td></td>
<td>• Post-approval for patients with certain serious diseases</td>
</tr>
</tbody>
</table>
General agreement that animal studies are necessary to understand toxicological effects.

The amount of data needed dependent on the effects and qualities of the product and human experience in similar drug classes – expected to vary among drug programs.

Animal models of disease useful in understanding disease mechanisms and obtaining information about the toxicological effects of drugs.
Additional considerations

- **Animal models of disease:**
  - Typically used to characterize pharmacodynamic (PD) action of drug
  - Potential to supplement or replace traditional toxicity study

- **Good Laboratory Practice (GLP) Studies**
  - Particular case specifics may preclude conduct according to GLPs
  - Data can still be supportive of safety assessment

- **Juvenile animal studies**
  - Clinical programs often initiate in pediatric populations
  - Supporting safety data in juvenile animal model is expected
  - Data to establish prospect of direct benefit (PDB)
FDA guidances that also provide insight

- FDA Draft Guidance for Industry: Antibacterial Therapies for Patients with Unmet Medical Need for the Treatment of Serious Bacterial Diseases (2013)
  - A sponsor developing a drug using a streamlined clinical development program must still provide adequate data to demonstrate that the drug is safe and effective
  - The other nonclinical studies may assume an even more important role

Summary

- From a safety perspective, rarity of disease generally does not influence the types of safety studies to be performed.

- Risk vs benefit is the primary consideration.
  - Benefit is not well characterized prior to Phase 3 trials.
  - Probability of benefit may outweigh safety concerns for serious and life-threatening diseases.

- 21 CFR 312 Subpart E: Drugs intended to treat life-threatening and severely-debilitating illnesses.
  - All safeguards designed to ensure safety of clinical testing apply to drugs covered by this section.
  - These include the review of animal studies prior to initial human testing.
Summary

- For serious and life-threatening diseases, the supporting nonclinical programs may look more like that described under ICH S9 than for M3(R2).
  - At a minimum, PD and single dose toxicity studies generally expected to support FIH single dose clinical trials

- Nonclinical review teams work closely with clinical reviewers to identify the appropriate balance of nonclinical data needed to support the safety of a given clinical program
Enzyme Replacement Therapies (ERTs) – a subset of therapies for rare diseases

- ERTs are unique among therapeutics in that they are intended to replace an enzyme that is deficient in patients.
  - the indication is usually a lysosomal storage disease

- ERTs are not intended to introduce novel pharmacological activity.

- ERTs are expected to have fewer unpredictable adverse effects than other products, based on the primary pharmacology.

- Since 2005, ERT programs evaluated by the Division of Gastroenterology and Inborn Error Products (DGIEP).
Key nonclinical challenges with ERT programs

- Understanding the impact of immunogenic (hypersensitivity) reactions on the study results and interpretation of data

- Unusual aspects of nonclinical study designs
  - Typical dosing frequency of once weekly or every other week in general toxicity studies; more frequent dosing in reproductive toxicity studies
  - Need for diphenhydramine pretreatment on dosing days to minimize hypersensitivity reactions, especially in rodents
  - Occasional use of disease models in safety studies
Key nonclinical challenges with ERT programs

- Use of “relevant species” concept as described in ICH S6(R1) to guide species selection for ERTs
  - demonstration of PD activity in normal animals is likely to be difficult or impossible
  - a disease model may be a relevant specie, but data interpretation may be difficult

- Animal disease models used for proof-of-concept studies to demonstrate PD activity
  - disease models can also provide important safety information related to excess production of substrate degradation products (i.e., primary pharmacology in the context of high substrate levels)
Review of FDA’s Nonclinical Requirements for Rare Disease Products: Focus on ERTs

- ERT programs often initiate with long-term clinical dosing trials
  - chronic studies were submitted to support FIH study in a majority of INDs

- DGIEP currently applies some flexibility in nonclinical requirements for products to treat inborn errors of metabolism, including ERTs

- DGIEP reviewing nonclinical database for ERTs to better understand observed safety signals and their impact on clinical development programs
DGIEP compiled a database of toxicology studies for 18 ERT products submitted to the Agency, to determine whether:

- new safety signals emerged from chronic studies (≥ 6-months) that were not identified in short-term studies (1-3 months)
- results of chronic studies were informative in predicting adverse effects in human trials
- results of chronic studies affected the study design, dose selection, and/or safety monitoring in FIH trials
Review of toxicology studies in ERT database

- In 3 of 13 (23%) INDs, adverse effects were observed in short-term toxicology studies.

- In 9 of 17 (53%) INDs, adverse effects were observed in chronic toxicology studies.

- In 5 of 13 (38%) INDs, potentially unique findings were observed in chronic toxicology studies that were not observed in the short-term studies. Majority of studies (4 of 5 INDs) used normal animals.
  - Examples of AEs emergent in chronic toxicology studies included: renal tubular degeneration, thrombus in atrium, and perivascular and alveolar hemorrhage.

- This summary excluded adverse effects that were clearly hypersensitivity reactions, but some effects captured in the database may have been secondary to immunogenicity.
Impact of chronic toxicology studies on FIH trials

- Investigational ERT-fusion protein:
  - Clinical protocol modified due to toxicities observed in the 26-week study in monkeys
  - Perivascular and alveolar hemorrhage led to reduction in starting dose
  - Hypoglycemia (including a death of one monkey due to severe hypoglycemia) led to frequent blood glucose monitoring
Considerations when interpreting the impact of toxicology studies on FIH ERT Trials

- Small sample size of available development programs
- Post-hoc exploration of the protocols does not allow the Agency to determine to what extent toxicology studies influenced the sponsor’s design of the FIH studies.
- Most IEM diseases result in multiple organ damage, so it can be challenging to distinguish between drug-related vs. disease-related effects.
- Toxicities seen in nonclinical studies help determine safe starting doses, and inform patients and investigators during drug development on potential safety signals.
Conclusions from survey of ERT database

- The value of chronic toxicology studies is still under assessment.

- Despite limitations that could have impacted interpretability of the information collected, toxicology studies were shown to impact FIH trials.

- A different standard for nonclinical study requirements may be considered for FIH studies and marketing approval for ERTs. Options include:
  - Case-by-case assessment
  - Develop a policy (guidance) that delineates different toxicity study requirements for rapidly progressing vs. indolent diseases
Future Directions

- Agency continues to evaluate the current testing paradigm
- Agency is assessing the adverse findings in chronic toxicity studies in the ERT database to evaluate the utility of chronic studies in supporting development of ERTs.
- Agency will consider the use of hybrid POC-safety studies in place of standard toxicology studies to support clinical trials.
Conclusions

- FDA is evaluating the minimal nonclinical requirements to support rare disease indications
  - “One size fits all” is not appropriate
  - Requirements determined by type of drug, clinical population, and proposed clinical trial

- FDA encourages sponsors to meet to obtain concurrence on a proposed nonclinical program to support FIH trials

- FDA is developing guidance for ERTs to assist sponsor’s in designing appropriate IND-enabling programs
Thank you!
Questions?