Development of Non-Traditional Therapies for Bacterial Infections
Pharmacology and Toxicology considerations

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Outline

1. Traditional nonclinical safety assessments during drug development
2. Special considerations for nontraditional therapies.
3. The future of nontraditional therapies.

The value of Nonclinical Pharmacology and Toxicology

1. Hazard identification
2. Hazard characterization
3. Risk assessment

Regulatory Guidances

- ICH M3(R2) ICH Guidance for Industry: M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals
- ICH S6(R1) ICH Guidance for Industry: S6 Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals
- FDA Estimating The Maximum Safe Starting Dose in Initial Clinical Trials For Therapeutics In Adult Healthy Volunteers (2005)
- ICH S2B Genotoxicity: A Standard Battery for Genotoxicity Testing for Pharmaceuticals; July 1997

First in Human Data Studies

- Pharmacodynamics
  - In vitro and/or in vivo studies
- Safety Pharmacology Studies
  - Cardiovascular System
  - Central Nervous System
  - Respiratory System
- PK/ADME (absorption, distribution, metabolism, & excretion)
- Genetic Toxicity Studies
  - Single clinical Doses
    - Gene mutation assay (i.e. in vitro Ames assay)
  - Multiple clinical Doses
    - Chromosomal damage in a mammalian system (i.e. in vitro chromosome aberration assay)
- General Toxicology Studies

Pharmacokinetics (ADME)

- ADME always useful to predict margins of safety
- Expected for traditional drugs
- No uniform guidelines for biotechnology-derived drugs.

- **Points to consider for nontraditional drugs**

- Delays in the expression of pharmacodynamic effects relative to the pharmacokinetic profile (e.g., cytokines)
- Prolonged expression of pharmacodynamic effects relative to plasma levels
- Alterations in the pharmacokinetic profile due to immune-mediated clearance mechanisms may affect the kinetic profiles and the interpretation of the toxicity data.
- Classic biotransformation studies not needed

Genotoxicity studies

Traditionally

- Single clinical doses
  - Gene mutation assay (i.e. *in vitro* Ames assay)
- Multiple clinical Doses
  - Chromosomal damage in a mammalian system (i.e. *in vitro* chromosome aberration assay)

Nontraditional drugs

- Traditional genotoxicity studies may not be needed for biopharmaceuticals.
- Biopharmaceuticals not expected to interact directly with the DNA or other chromosomal material
- Large quantities of peptides/proteins may yield uninterpretable results

Immunogenicity

- Many biotechnology-derived pharmaceuticals are immunogenic in animals.

- Antibody responses should be characterized in repeated dose toxicity studies
  - Titer, number of responding animals, neutralizing or non-neutralizing)
  - Timing should be correlated with any pharmacological and/or toxicological changes

- The detection of antibodies should not be the sole criterion for the early termination of a preclinical safety study or modification in the duration of the study design **unless the immune response neutralizes the pharmacological and/or toxicological effects** of the biopharmaceutical in a large proportion of the animals.

- In most cases, the immune response to biopharmaceuticals is **variable**, like that observed in humans.
- ICH S8

ICH M3(R2): General Toxicology Studies to Support Early Clinical Trials

- **Acute Toxicology**
  - 2 species
    - 1 rodent + 1 non-rodent
  - Either single dose or repeat dose studies that test to a maximum tolerated dose (MTD)

- **Repeat-Dose Toxicology**
  - ≥2-week in 2 species
    - 1 rodent + 1 non-rodent

- Include most relevant species
  - pharmacologically active
  - Target distribution information is useful

- High Dose
  - MTD
  - Maximum feasible dose (MFD)
  - Saturation of exposure
  - Limit dose
    - ≤1 g/day : 1000 mg/kg/day
    - >1 g/day: 2000 mg/kg/day or MFD
  - Large exposure multiple
    - 50-fold margin based on exposure is generally sufficient

General Tox Study Duration ≥ Clinical Trial Duration

(Early Phase ≤ 6 months)

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

Maximum Duration of Clinical Trial	Recommended Minimum Duration of Repeated-Dose Toxicity Studies to Support Clinical Trials	
	Rodents	Nonrodents
Up to 2 weeks	2 weeks[a]	2 weeks[a]
Between 2 weeks and 6 months	Same as clinical trial[b]	Same as clinical trial[b]
> 6 months	6 months[b, c]	9 months[b, c, d]

a. In the United States, as an alternative to 2-week studies, extended single-dose toxicity studies (see footnote c in Table 3) can support single-dose human trials. Clinical studies of less than 14 days can be supported with toxicity studies of the same duration as the proposed clinical study.

[Table 1, ICHM3(R2)]

Relevant species

- A relevant species is one in which the test material is **pharmacologically active** due to the expression of the **receptor** or an **epitope** and demonstrate a similar **tissue cross-reactivity** profile as for human tissues.

- When no relevant species exists, the use of relevant **transgenic animals** expressing the human receptor or the use of **homologous proteins** should be considered.

- **However**, the production process, range of impurities/contaminants, pharmacokinetics, and exact pharmacological mechanism(s) may differ between the homologous form and the product intended for clinical use.

- A **limited toxicity evaluation in a single species**, e.g., a repeated dose toxicity study of $\leq$ 14 days duration that includes an evaluation of important functional endpoints (e.g., cardiovascular and respiratory) may be useful in the absence of transgenic animal models or homologous proteins.

Two species

- Normally include two relevant species.
- One species may suffice
  - If only one relevant species can be identified or
  - where the biological activity of the biopharmaceutical is well understood.
  - Study is a long term toxicity study and the toxicity profile in the two species is comparable in the short term.

Nonclinical toxicology combination studies

- **Recommended if:**
  - Individual agents are only intended for use in combination (copackaged or fixed formulation or products with recommendations for co-use) + complete nonclinical development programs not conducted on the individual entities)
  - Two early stage drugs
  - Significant toxicological concern (e.g., similar target organ toxicity).
  - Low margins of safety
  - Adverse effects that are difficult to monitor in humans.
  - For combinations of an early stage entity(ies) with clinical experience with a late stage entity(ies)…….Later stage or longer duration clinical studies should be supported by a nonclinical combination toxicity study.

Nonclinical toxicology combination studies

- Prior to clinical studies if there is a significant toxicological concern.
- A single relevant species.
- Duration of the combination study should be equivalent to that of the clinical trial, up to a maximum duration of 90 days.
- If unexpected toxicity is identified, additional testing can be appropriate.

Nonclinical toxicology combination studies

- **Not recommended**
  - Early stage entity with clinical experience with a late stage entity(ies), for which there is no significant toxicological concern, combination toxicity studies are not recommended to support clinical proof-of-concept studies of up to one month duration.
  - Two late stage entities + adequate clinical experience with co-administration.
  - Genotoxicity/Safety Pharmacology/Carcinogenicity studies (if the individual agents have been tested according to current standards).

Preclinical Data & Therapeutic Window Predictions

NOAEL = No Observed **Adverse** Effect Level

* "…the highest dose level that does not produce a significant increase in adverse effects in comparison to the control group"

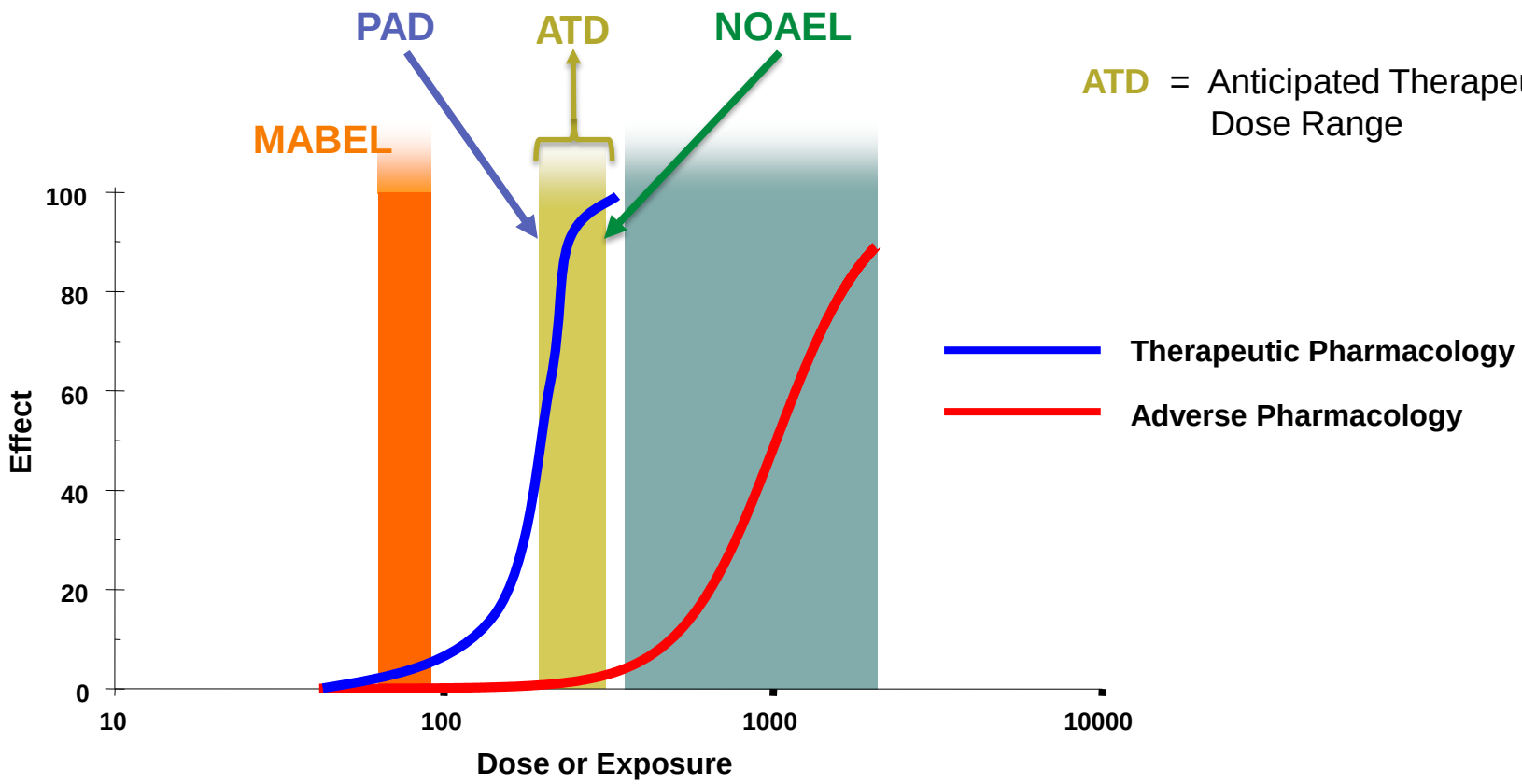
- Determined empirically in GLP toxicology and safety pharmacology studies in animals

MABEL = Minimal Anticipated Biological Effect Level

- *In vitro* pharmacology data from target cells from human and toxicology species
- Concentration-effect data from *in vitro* and *in vivo* studies
- Integrate data into PK/PD model (if feasible), to predict pharmacological response in humans at multiple dose levels

PAD = Pharmacologically Active Dose

ATD = Anticipated Therapeutic Dose Range



* (FDA Guidance for Industry: Estimating The Maximum Safe Starting Dose in Initial Clinical Trials For Therapeutics In Adult Healthy Volunteers)

Nonclinical Studies: Support Late Phase (≥ Phase 3)

ICH M3 (R2)

Small Molecules

- PD
- Safety Pharmacology
- PK & Protein Binding
- ADME
- General Toxicology
  - 6 month rodent - **AND** -
  - 9 month non-rodent
- Genetic Toxicity
  - Complete prior to Phase 2
- Carcinogenicity
- Reproductive & Developmental Tox

ICH S6 (R1)

Biologics

- PD
- Safety Pharmacology
- PK
  - Protein Binding (if applicable)
- General Toxicology
  - ≤1 month in 2 species
  - Chronic 6 month rodent
    – **OR** – 6 month non-rodent
- Carcinogenicity
- Reproductive & Developmental Tox

Reproductive toxicity

- Conducted in accordance with the principles outlined in ICH S5(R2) Guideline based on an understanding of species specificity, the nature of the product and mechanism of action, immunogenicity and/or pharmacokinetic behavior and embryo-fetal exposure.

- The evaluation of toxicity to reproduction should be conducted only in pharmacologically relevant species.

- For products that are directed at a foreign target such as bacteria and viruses, in general no reproductive toxicity studies would be expected (ICH S6).

- There may be extensive public information available regarding potential reproductive and/or developmental effects of a particular class of compounds.

Carcinogenicity studies

- Long duration regimen
  - 6 months continuous or repeated intermittent dosing should be conducted to support the marketing application.

- Significant concern for carcinogenic risk
  - Study should be submitted to support clinical trials.

ICH S1A and ICH M3 (R2)

The Future-Animal models of disease

- Traditional Nonclinical Toxicology studies conducted in healthy animals.
- Animal models of human disease may provide further insight into:
  - Pharmacology
  - Pharmacokinetics,
  - Dosimetry,
  - Formulation
  - Routes
  - Treatment regimen
  - Toxicity endpoints
  - Safety (e.g., evaluation of undesirable promotion of disease progression).
  - The scientific justification should be provided
  - The collection of concurrent control and baseline data is critical.
  - ICH S6

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Thank you for you attention!

Questions?


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