Preclinical Development to IND: Drugs and Vaccines

Maralee McVean, PhD
Vice President, Pharmacology and Toxicology Services
PreClinical Research Services, Inc.
maralee.mcvean@preclinicalresearch.com
Overview

• Challenges and components of early drug development
• Nonclinical testing and timelines
• Regulatory standards for studies
• Elements of preclinical/nonclinical studies needed for IND filing
• Special considerations for Biologics and Vaccines
• IND preparation and filing
Challenges of Drug Development

- 200 enter Phase 1 (0.67%)
- 8 survive to approval (0.03%)
- 1 (0.003%) makes a satisfactory return on investment of 10-12 years of work costing $500 mm

DDT Vol 6 2001
Basics Steps of Drug Discovery

• Identifying target
• Finding “hit” compounds
  • Setting goals for therapeutic area
  • Screening and progression criteria
  • Primary screens
• Physiochemical and ADME properties
• Selectivity and Safety Screens
• In vivo studies
  • Pharmacokinetics and excretion
  • Efficacy models
  • Toxicological assessment
Nonclinical Planning Essential

• Nonclinical vs Preclinical
• All non-\textit{in vivo} human studies
  • i.e., all \textit{in vivo} animal studies, and all \textit{in vitro} studies
• Includes:
  • Pharmacology (\textit{in vivo} and \textit{in vitro})
  • \textit{In vivo} animal efficacy
  • Pharmacodynamics
  • PK/ADME
  • Toxicology/TK

PK = pharmacokinetics
ADME = absorption/distribution/metabolism/excretion
TK = toxicokinetics
### Preclinical and Nonclinical Studies

#### Preclinical Testing

<table>
<thead>
<tr>
<th>nonGLP and GLP animal testing</th>
<th>Pharmacology</th>
<th>Efficacy studies</th>
<th>Pharmacokinetics</th>
<th>ADME</th>
<th>Excretion</th>
<th>P450 inhibition/induction</th>
<th>In vitro metabolism</th>
<th>Allometric scaling</th>
<th>Safety Pharmacology</th>
<th>Cardiocvascular</th>
<th>CNS</th>
<th>Respiratory</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Gene Tox</td>
<td>Ames test</td>
<td>Chromosome aberration</td>
<td>Local tolerance</td>
<td>Eye/skin irritation</td>
<td>Toxicology in 2 species:</td>
<td>Toxicokinetics</td>
<td>Identify:</td>
<td>Target organ</td>
<td>NOAEL</td>
<td>MTD</td>
<td>Therapeutic Index</td>
</tr>
<tr>
<td>Pharmacology</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Single-dose tox</td>
<td></td>
<td>Target organ:</td>
<td>NOAEL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Efficacy studies</td>
<td>Gene Tox</td>
<td>Ames test</td>
<td>Chromosome aberration</td>
<td>Local tolerance</td>
<td>Eye/skin irritation</td>
<td>Repeat-dose tox</td>
<td></td>
<td>Target organ:</td>
<td>NOAEL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pharmacokinetics</td>
<td>Gene Tox</td>
<td>Ames test</td>
<td>Chromosome aberration</td>
<td>Local tolerance</td>
<td>Eye/skin irritation</td>
<td>(2 weeks to 3 months)</td>
<td></td>
<td>Therapeutic Index</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADME</td>
<td>Gene Tox</td>
<td>Ames test</td>
<td>Chromosome aberration</td>
<td>Local tolerance</td>
<td>Eye/skin irritation</td>
<td>Toxokinetics</td>
<td></td>
<td>Therapeutic Index</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Excretion</td>
<td>Gene Tox</td>
<td>Ames test</td>
<td>Chromosome aberration</td>
<td>Local tolerance</td>
<td>Eye/skin irritation</td>
<td>Identify:</td>
<td></td>
<td>Therapeutic Index</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P450 inhibition/induction</td>
<td>Gene Tox</td>
<td>Ames test</td>
<td>Chromosome aberration</td>
<td>Local tolerance</td>
<td>Eye/skin irritation</td>
<td></td>
<td></td>
<td>Therapeutic Index</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In vitro metabolism</td>
<td>Gene Tox</td>
<td>Ames test</td>
<td>Chromosome aberration</td>
<td>Local tolerance</td>
<td>Eye/skin irritation</td>
<td></td>
<td></td>
<td>Therapeutic Index</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Allometric scaling</td>
<td>Gene Tox</td>
<td>Ames test</td>
<td>Chromosome aberration</td>
<td>Local tolerance</td>
<td>Eye/skin irritation</td>
<td></td>
<td></td>
<td>Therapeutic Index</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### Clinical Testing / Nonclinical Testing

<table>
<thead>
<tr>
<th>IND</th>
<th>GLP animal testing</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Metabolism</td>
</tr>
<tr>
<td></td>
<td>Distribution (radiolabel)</td>
</tr>
<tr>
<td></td>
<td>Subchronic tox</td>
</tr>
<tr>
<td></td>
<td>Chronic tox</td>
</tr>
<tr>
<td></td>
<td>(rats-6 month, dog/primate 9 months)</td>
</tr>
<tr>
<td></td>
<td>Toxicokinetics</td>
</tr>
<tr>
<td></td>
<td>DART:</td>
</tr>
<tr>
<td></td>
<td>Seg II – rat/rabbit teratogenicity</td>
</tr>
<tr>
<td></td>
<td>Seg I – male/female fertility</td>
</tr>
<tr>
<td></td>
<td>Seg III - pre- and post-natal</td>
</tr>
<tr>
<td></td>
<td>Carcinogenicity (rat/mouse)</td>
</tr>
<tr>
<td></td>
<td>Special studies:</td>
</tr>
<tr>
<td></td>
<td>Immunotoxicity</td>
</tr>
<tr>
<td></td>
<td>Comparability studies</td>
</tr>
</tbody>
</table>

#### NDA | Phase I-III Clinical Trials
New Drug Development Timeline

Preclinical testing
- 1-5 years
- Drug synthesis Formulation Stability
- CMC
- GLP animal testing
- IND-enabling

Clinical testing / Nonclinical Testing
- IND
- 5 years (2-10)
- CMC – chemistry manufacturing and controls
- NDA-enabling
- patient testing
- Phase I
- Phase II
- Phase III
- open-label extension
- Phase IV

NDA review
- 2 years (2 months – 7 years)

Post-approval surveillance
- End of Phase II meeting
- Pre-NDA/BLA meeting
- NDA/BLA submitted
- NDA/BLA approved

Industry time
- pre-IND meeting
- 30-day IND review
- IND submitted
- End of Phase II meeting
- Pre-NDA/BLA meeting

FDA time
- NDA/BLA submitted
- NDA/BLA approved
Nonclinical Safety Packages

- “Normal” indications
  - Non-advanced cancer
  - Non-life-threatening
- Cancer
  - Serious, advanced and life threatening malignancies
  - Patient has failed standard of care and cancer is progressing
  - Patient has limited life expectancy
- Safety studies
  - Stand alone safety pharmacology not necessary
  - Demonstrate dose limiting toxicity
  - NOEL/NOAEL not essential
  - One month duration sufficient to enable Phase I and II clinical trials (clinical judgment ongoing)
  - 3 month studies needed before start of Phase III
- Carcinogenicity studies generally not needed
- Genotoxicity needed for NDA only
- Seg II (Teratogenesis) possibly needed; No need for Seg I or III
Nonclinical safety assessment for marketing approval include:

- Safety pharmacology studies, general toxicity studies, toxicokinetic and pharmacokinetic studies, reproduction toxicity studies, genotoxicity studies
- Carcinogenicity potential for drugs having special cause for concern or are intended for chronic use
- Studies to assess phototoxicity, immunotoxicity, juvenile animal toxicity and abuse liability conducted on a case-by-case basis
Nonclinical Safety Testing – What’s Required?

- **Goals:**
  - Characterize toxic effects with respect to
    - Target organs
    - Dose dependence
    - Relationship to exposure
    - Potential reversibility

- **Information is used to**
  - Estimate an initial safe starting dose and dose range for the human trials
  - Identify parameters for clinical monitoring for potential adverse effects.

- **Studies should be thorough enough to adequately characterize potential AEs that might occur under the conditions of the clinical trial to be supported**
  - “Dose for dose” paradigm
  - Same route of administration
GLP Regulated Studies

- Good Laboratory Practice (1976) 21 CFR – Part 58
  - Govern how to perform studies:
    How studies are planned, performed, monitored, recorded, and reported.
- All studies that support assessment of safety are required to be GLP
  - Not required - e.g., drug discovery, efficacy studies, PK studies, preliminary toxicology studies, most ADME studies, investigational toxicology studies
  - Required - e.g., pivotal toxicology studies, PK studies, bioanalytical of TK samples, safety pharmacology, genotox, reprotox, carcinogenicity
- Independent quality assurance (QA) unit oversight
- All routine work and facility operations must follow written standard operating procedures (SOPs)
- Responsibilities defined for sponsor management and study management (study director)
- Test article (TA) and vehicle must be fully characterized
- Identity, purity, stability, homogeneity and concentration of test article must be demonstrated prior to dosing and be adequate for the duration and storage conditions of the study
- Instruments are to be calibrated and maintained
- Personnel require proper qualification and training
- Raw data and other data need to be acquired, processed and archived to ensure integrity of the data
Pharmacokinetic / Toxicokinetics

- PK - Pharmacokinetics
  - PK profile of efficacious doses

- TK - Toxicokinetics
  - PK profile at high doses

- Endpoints
  - $C_{\text{max}}$
  - $t_{\text{max}}$
  - AUC (area under the curve)
  - Clearance
  - Volume of Distribution
  - Bioavailability - percent of drug that is absorbed relative to the maximum absorbed seen after IV dosing

![Concentration vs Time Graph]

- iv 3 mg/kg
- po 10 mg/kg
Toxicology Evaluation

- Appropriate species – one rodent, one second species (dog, pig or monkey generally)
  - Good exposure
  - Metabolism similar to human – must cover all human metabolites
  - Same pharmacologic activity as humans (same target binding, effect in disease models, pharmacologic effects)
- Exposures achieved in test species should be sufficient to cover multiples of the intended human dose/exposure in order to establish a safety margin
- Higher doses to evaluate possible toxicities that could occur
  - FDA guidance to dose up to 1 g/kg, if possible
- Administer compound long enough to support intended clinical study
- Example endpoints: body weight, clinical observations, serum chemistry, hematology, organ weights, histology, drug exposure (toxicokinetics)
Nonclinical Safety Testing – Duration of Dosing

<table>
<thead>
<tr>
<th>Maximum Duration of Clinical Trial</th>
<th>Rodent</th>
<th>Non-Rodent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Up to 2 weeks</td>
<td>2 weeks&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2 weeks&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>&gt;2 weeks to 6 months</td>
<td>Same as clinical trial&lt;sup&gt;b&lt;/sup&gt;</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>
<td>9 months&lt;sup&gt;b,c,d&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup> US - extended single-dose toxicity studies can support single-dose human trials.

<sup>b</sup> Clinical trials > 3 months can be initiated if complete in-life data (and histo from rodent) are available from a 3-month rodent and a 3-month non-rodent study prior to getting to 3 months in humans.

<sup>c</sup> Histo from the non-rodent should be available within an additional 3 months.

<sup>d</sup> Peds- juvenile animals may be needed.

<sup>e</sup> EU – 6 months studies in non-rodents acceptable.

US and Japan - OK if:
- Immunogenicity/tox confounds longer studies
- Clinical indication with intermittent dosing (migraine, HSV..)
- Cancer
- Short life expectancy

<sup>2009 M3(R2) Guidance</sup>

BioBoot Camp, April 2013
Nonclinical Safety Testing – Duration of Dosing

Recommendations to Support Marketing

<table>
<thead>
<tr>
<th>Duration of Indicated Treatment</th>
<th>Rodent</th>
<th>Non-Rodent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Up to 2 weeks</td>
<td>1 month</td>
<td>1 month</td>
</tr>
<tr>
<td>&gt;2 weeks to 1 month</td>
<td>3 months</td>
<td>3 months</td>
</tr>
<tr>
<td>&gt;1 month to 3 months</td>
<td>6 months</td>
<td>6 months</td>
</tr>
<tr>
<td>&gt;3 months</td>
<td>6 months</td>
<td>9 months</td>
</tr>
</tbody>
</table>

2009 M3(R2) Guidance
PK/TG Bioanalytical

- Crucial to demonstrate exposure levels in toxicology studies – human starting doses are based on this data!
- Small molecules - HPLC/MS
  - Can definitively show the molecular structure
- Biologics - ELISA
  - Does not show structure
  - Uses binding as an endpoint
  - Does not demonstrate activity
- Assay needs to be validated for use in GLP studies and be performed GLP
  - Extraction technique recovery
  - Linearity of standard curve
  - Intra- and inter-assay precision
  - Bench top and freeze/thaw stability
  - Sensitivity (lower limit of quantitation; LOQ)
  - Establish Quality Control (QC) standards
Nonclinical Safety Testing – Endpoints

- Clinical observations
- Clinical pathology
- Body weights
- Food consumption
- Gross findings/lesions
- Organ weights
- Histopathology – often definitive
- TK
Nonclinical Safety Testing – Safety Pharmacology

- 1st Tier (Core Battery)
  - Respiratory
  - Cardiovascular
  - CNS – Irwin Test (FOB – functional observational battery)
- 2nd Tier (Supplementary)
  - Renal
  - GI
  - Autonomic nervous System
  - Other (e.g., immune, skeletal muscle, endocrine)

2000 ICH S7A
Nonclinical Safety Testing – Genotoxicity

- Minimum prior to Single Dose Study:
  - Ames Test for mutations
- Minimum Prior to Multiple Dose Study:
  - Chromosomal Abnormalities (e.g., mouse lymphoma)
- Prior to Phase 2:
  - 2nd Chromosomal Abnormalities (mouse micronucleus)

2009 M3(R2) Guidance
Nonclinical Safety Testing – Other

- Local Tolerance
  - Skin
  - Eye
  - GI (Stomach)
- Immunotoxicity
- Phototoxicity
- Dependence/Abuse potential

2009 M3(R2) Guidance
Human Maximum Recommended Starting Dose (MRSD)

- Using animal toxicity data to calculate the starting dose in the first in man (FIM) Phase I trial
- Convert animal dose to human dose on a mg/m^2 body surface area basis
- Procedure:
  - Determine NOAEL for all toxicology species
  - Determine the most appropriate species
  - Convert NOAEL in mg/kg to Human Equivalent Dose (HED)
  - Multiplication Factors:
    - Mouse = 3
    - Rat = 6
    - Monkey = 12
    - Dog = 20
- Example: a 30 mg/kg dose in the monkey converts to 360 mg/m^2. Avg human BSA = 1.67 m^2. So the HED = 1.67 * 360 = 601.2 mg
- Apply appropriate safety factor
  - FDA recommends 10-fold as a standard for non-oncology drugs
  - Make adjustments to the starting dose if data warrant
10-Fold Safety Factor Exceptions

• Increasing the Safety Factor
  • Steep toxicity dose response curve
  • Severe, irreversible toxicity
  • Non-monitorable toxicity
  • Toxicity without pre-monitory signs
  • Expected variable bioavailability in the clinic
  • Unexplained mortality in the animal studies
  • Nonlinear PK
  • Inadequate dose response data
  • Novel therapeutic target
  • Animal models with limited utility

• Decreasing the Safety Factor
  • Drug is from a well characterized class of drugs
  • Toxicities easily monitored, reversible, non-severe, predictable, and shallow dose-response
Biologics - Differences with small molecules

- Protein structure, highly targeted and specific, inactive metabolites
- Bioanalytical
  - LC/MS/MS versus ELISA assays
  - Need to test for anti-test article antibodies
- Manufacturing
  - Complexity of protein structure results in heterogeneity of final product
  - Glycosylation, oxidation, disulfide bonds, aggregation, etc.
  - Scale up may alter product
  - Functional assays often needed
- Immunogenicity
  - Anaphylaxis
  - Immune complexes - glomerulonephritis
  - Anti-test article antibodies can:
    - Affect activity (increase or decrease)
    - Cross react with endogenous proteins
  - In animals not necessarily predictive of humans
- Relevant species may be limited (e.g., NHP)
  - Non-human primate (NHP) such as cynomolgus and rhesus monkeys
  - Limitations for reprotox, carcinogenicity, host resistance studies
  - More expensive, can be harder to obtain
  - Ethical issues
GLP requirements for studies are the same. Tissue cross-reactivity studies are needed for monoclonal antibodies, assessing the ability to bind to target and non-target tissues. Some areas may not be required, such as metabolism, limited safety pharmacology, genotoxicity, and carcinogenicity. Toxicity is usually due to exaggerated pharmacology. The highest dose in toxicology studies should be a scientifically reasonable multiple of the highest projected clinical dose, the maximum feasible dose, or a dose reflective of a pharmacodynamic marker, like saturation of antigen. The Minimal Anticipated Biological Effect Level (MABEL) is determined from animal efficacy/PK data and in vitro data, potentially being lower than the Minimal Risk Surface Dose (MRSD).
Vaccines – General Considerations for Toxicology Assessment

• What is not needed:
  • Genotox generally not necessary, but required for new adjuvants
  • Carcinogenicity

• Provides evidence for the safety of the vaccine and identifies a NOAEL
• Identifies any potential toxicities and target organs

• Caveats:
  • Rare sub-population toxicity is only addressable in humans
  • Animal models not always indicative of the effect in humans

• Additional endpoints in toxicology studies/other studies:
  • Protection upon challenge in appropriate animal model
  • Immunogenicity – antibody class, avidity, affinity, titer, half-life, functionality
  • Seroconversion rates, activation of cytokine secretion, other cell mediated immune response
  • Persistence of DNA plasmid in vaccine in tissues
  • Novel adjuvants may need stand alone testing
pre-IND Meeting - Information Package

- Pre-IND consultation contacts
- Send to FDA 4 weeks prior to meeting
- Table of Contents:
  - Product name and chemical structure
  - Proposed indication
  - Dose form, route and dosing regimen
  - Purpose of the meeting
  - Objectives
  - Background – data to date
  - CMC plan
  - Nonclinical plan
  - Clinical Phase I protocol
- List of questions:
  - CMC
  - Nonclinical
  - Clinical
Filing the IND

- Electronic format – Common Technical Document
- Includes:
  - Animal Pharmacology and Toxicology Studies
  - Manufacturing Information
  - Clinical Protocols and Investigator Brochures
- FDA sends letter acknowledging receipt of the submission and assigns the IND number
- Review period of 30 calendar days before initiating any clinical trials
- If there are no issues, the IND generally goes into effect 30 days after the *Date of Receipt* shown in letter
Abbreviations

- ADME = absorption/distribution/metabolism/excretion
- IND = Investigational New Drug application
- NOEL/NOAEL = No Observed Effect Level/No Observed Adverse Effect Level
- MABEL = Minimal Anticipated Biological Effect Level
- NDA = New Drug Application
- BLA = Biologic License Application
- MTD = Maximum tolerated dose
- CMC = Chemistry manufacturing controls
- MRSD = Maximum Recommended Starting Dose
References

FDA Guidances

ICH documents on nonclinical studies to support drug development:
M3(R2) Nonclinical safety studies for the conduct of human clinical trials and marketing authorization for pharmaceuticals

S9 Nonclinical evaluation for anticancer pharmaceuticals

S6 Preclinical safety evaluation of biotechnology derived pharmaceuticals

Vaccines

Providing regulatory submissions in electronic format

CRF 21 – part 58
http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=58&showFR=1
Questions?

Maralee McVean, PhD
Vice President, Pharmacology and Toxicology Services
PreClinical Research Services, Inc.

Maralee.mcvean@preclinicalresearch.com
970-658-7666