Preclinical Development to IND: Drugs, Biologics, Cellular/Gene Therapies and Vaccines

BioBoot Camp
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Background and Disclosures

- PhD at University of AZ in Pharmacology/Toxicology
- Post-doctoral appointment at KUMC in Kansas City
- Drug Discovery and Development since 2000
  - Small to mid-sized pharma
  - Diverse therapeutic areas including cancer, inflammatory disorders, anti-virals, pain and diabetes
  - Multiple INDs to Phase I trials
- Joined PreClinical Research Services in 2011
- This presentation is not an official regulatory guidance and discussions with the FDA are encouraged!
Overview

- Challenges and components of early drug discovery and development
- Nonclinical testing and timelines
- Regulatory standards for studies
- Elements of preclinical studies needed for IND filing
- Special considerations for Biologics, Vaccines and Cellular/Gene Therapies
- IND preparation and filing
Economic and Scientific Challenges of Drug Development

The Pharmaceutical Research and Manufacturers of America (PhRMA) estimates to get a new medicine to market:

- Costs a company at least $1.2 billion
- 10-15 years of discovery/development
- For every 5,000 to 10,000 compounds that enter the pipeline, only one receives approval
- Even medicines that reach clinical trials have only a 16% chance of being approved
- R&D budgets are shrinking due to assorted economic factors
  - PhRMA’s 2013 progress report found that R&D spending by its members peaked at $50.7 billion in 2010
  - Dropped to $48.6 billion in 2011 and an estimated $48.5 billion in 2012
Basics Steps of Drug Discovery

• Identifying target
• Finding “hit” compounds
  • Setting goals for therapeutic area
  • Screening and progression criteria
  • Primary screens
• Preclinical/Nonclinical Studies
  • In vitro studies in animal and human systems and in vivo animal studies
  • Determine systemic uptake and exposure, metabolism, pharmacological effect, potential toxicities and target organs of a drug
• In vitro Physiochemical and ADME properties
• Selectivity and Safety Screens
• In vivo studies
  • Pharmacokinetics and ADME
  • Efficacy models
  • Toxicological/Safety assessment
# Preclinical and Nonclinical Studies

## Preclinical Testing

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<th>nonGLP and GLP animal testing</th>
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<td>Pharmacology</td>
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<td>ADME</td>
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<td>Absorption</td>
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<td>Distribution</td>
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<td><em>In vitro</em> metabolism</td>
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<td>Cardiovascular</td>
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<td>CNS</td>
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<td>Respiratory</td>
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## Clinical Testing / Nonclinical Testing

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

**Preclinical testing**
- IND submitted
- 30-day IND review
- Pre-IND meeting

**Clinical testing / Nonclinical Testing**
- Drug synthesis
- Formulation
- Stability
- CMC
- GLP animal testing
- IND-enabling
- NDA-enabling
- patient testing

**IND**
- 1-5 years

**Clinical testing / Nonclinical Testing**
- CMC – chemistry manufacturing and controls
- NDA review
- Post-approval surveillance

**Phase I**
- End of Phase II meeting
- Pre-NDA/BLA meeting
- NDA/BLA submitted
- NDA/BLA approved

**Phase II**
- 2 years
- (2 months – 7 years)

**Phase III**
- 5 years (2-10)

**Phase IV**
- open-label extension

**Phase V**
- Industry time
- FDA time

**Post-approval surveillance**
- NDA review
ADME - Importance of Drug Metabolism

- Drug metabolism is the biochemical transformation of a compound to another chemical form enabling removal of drugs from the body
- Important factors
  - Metabolite toxicity
  - Rapid metabolism affects dosing regimen
  - Drug that is NOT readily metabolized will have a prolonged circulation time which may influence safety
  - Drug-drug interactions
- FDA requires that the effects of a drug on the metabolism of other drugs and the effects of other drugs on a drug’s metabolism should be assessed relatively early in drug development so that the clinical implications of interactions can be assessed
Drug Metabolism Assay Requirements

• Required for the IND
  • Plasma protein binding
  • In vitro metabolic profile
    • Stability of compound affects exposure
    • Tox species and human
    • Microsomes or hepatocytes

• P450* metabolism - Not required at IND filing, but important info!
  • P450’s have Polymorphic Distribution - A trait that has differential expression in >1% of the population
  • Different people will have different metabolism of compounds
  • Drug/drug interactions will be different too
  • P450 enzyme inhibition
  • P450 enzyme induction
  • Metabolite identification – may have toxicity too!

*P450 enzymes – drug metabolizing enzymes
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
Species Specific PK

- PK parameters can vary significantly between species
- Identify species that more closely reflect predicted human exposure and metabolism

![Rat](image1)

![Dog](image2)

![Monkey](image3)

![Human](image4)
Efficacy Testing in Animal Models

- In vivo testing in an animal model to demonstrate an effect on the target or on disease outcome
- Choose relevant animal model for therapeutic area
  - Tumor growth inhibition
  - Inflammation scoring
  - Pain measurements
- Prefer short term dosing, acute (single dose)
- PK acceptable in chosen species
- Dose at concentrations expected to result in good exposure
- Dose response to confirm pharmacological mechanism
- Find lowest dose that gives desired efficacy
- May want to evaluate drug in multiple animal models
Biomarker Identification and PK/PD

- Biomarkers used to measure pharmacologic responses to a therapeutic treatment
- The biomarker can be used to measure a pharmacodynamic (PD) effect (biological effect over time)
- PK/PD is used to relate the biological effect to drug concentrations
- Examples:
  - Toxicity biomarkers can include elevated liver or kidney enzymes indicative of cellular damage and enzyme release
  - Cellular kinase inhibition used to measure activity of drug in vivo
- Can be used clinically to monitor/predict safety and efficacy
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 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
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
  • Toxicology/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
  • Development and Reproductive Tox - Seg II (Teratogenesis) possibly needed; No need for Seg I or III
GLP Regulated Studies

- Good Laboratory Practice (1976) 21 CFR – Part 58
  - Ensure quality and integrity of study data
  - Governs how studies are planned, performed, monitored, recorded, and reported
- All studies that support assessment of safety are required to be GLP
- 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 must be calibrated and maintained
- Personnel require proper qualification, training and records thereof
- Raw data and other data need to be acquired, processed and archived adequately to ensure reliability of the data
What needs to be GLP vs nonGLP?

**GLP**
- Pivotal Safety Pharmacology and Toxicology studies
- Bioanalysis*
- Dose solution analysis*
- Gene tox
- Repro tox
- Carcinogenicity

*If run non-GLP, a compelling justification should be included in protocols for GLP studies

**Can be non-GLP**
- PK studies
- Drug metabolism studies
- Efficacy studies
- Preliminary or investigational toxicology studies
Safety Screens – Mutagenicity and Mammalian Genotoxicity

- **Ames Test**
  - Bacterial strains with enhanced sensitivity to some mutagens
  - When exposed to a mutagenic compounds, bacteria revert from histidine dependence to histidine independence
  - Mutated bacteria will grow more colonies than non-mutated bacteria
  - Compounds may be mutagenic or may need to be metabolized for mutagenicity
    - Addition of rat liver extract allows for metabolism

- **In vitro cell culture systems**
  - Mutations
  - Chromosomal damage

- **In vivo systems**
  - Chromosomal damage

- **DNA damage and repair**
  - DNA breakage
  - Unscheduled DNA synthesis

- **Carcinogenesis studies** – occur later in development
Timing of Safety Testing – Genotoxicity

• Minimum prior to Single Dose Study in Humans:
  • Bacterial mutagenicity (Ames Test for mutations)
• Minimum Prior to Multiple Dose Study in Humans:
  • Chromosomal Abnormalities (mouse lymphoma cells
    or human/CHO chromosome aberration assay)
• Prior to Phase 2 Clinical Trials:
  • 2\textsuperscript{nd} Chromosomal Abnormalities (\textit{in vivo} rodent
    micronucleus assay)
Nonclinical Safety Testing – Safety Pharmacology

• 1\textsuperscript{st} Tier (Core Battery)
  • Can be built into main tox study
  • Respiratory
  • Cardiovascular
  • CNS – Irwin Test or FOB (functional observational battery)

• 2\textsuperscript{nd} Tier (Supplementary)
  • Dependence/Abuse potential
  • Renal
  • GI
  • Autonomic nervous System
  • Other (e.g., immune, skeletal muscle, endocrine)

2000 ICH S7A
Safety Pharmacology – CV Safety

- Normal heartbeat includes QT interval (repolarization)
- hERG blockers
  - Prolongation of the QT interval which is associated with rare life-threatening arrhythmia, Torsades de pointes
  - QT prolongation is most often associated with inhibition of the rapid delayed rectifier potassium current ($I_{Kr}$) which is associated with the hERG (human ether-a-go-go gene) channel.
- Cells overexpressing hERG or cultured cardiac myocytes
- Other cardiac channels can also be assessed
- Telemetry / ex vivo studies
Pivotal Toxicology Studies - What’s Required for IND filing?

- Appropriate species – one rodent, one second species (dog, minipig 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, feed consumption, clinical observations, clinical pathology, organ weights, gross findings at necropsy, histopathology (often definitive), drug exposure (TK)
Nonclinical Safety Testing – Duration of Dosing

<table>
<thead>
<tr>
<th>Maximum Duration of Clinical Trial</th>
<th>Recommended Minimum Duration of Repeat-Dose Tox Studies to Support Clinical Trial</th>
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<tbody>
<tr>
<td>Rodent</td>
<td>Non-Rodent</td>
</tr>
<tr>
<td>Up to 2 weeks</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>
</tr>
<tr>
<td>&gt;6 months</td>
<td>6 months&lt;sup&gt;b,c&lt;/sup&gt;</td>
</tr>
<tr>
<td></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. Histo from the non-rodent should be available within an additional 3 months.

<sup>c</sup> Peds- juvenile animals may be needed

<sup>d</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

2010 M3(R2) Guidance
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>
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<tr>
<td>&gt;2 weeks to 1 month</td>
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<td>6 months</td>
</tr>
<tr>
<td>&gt;3 months</td>
<td>6 months</td>
<td>9 months</td>
</tr>
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PK/TK 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
Human Maximum Recommended Starting Dose (MRSD)

- Using animal toxicity data to calculate the starting dose in the first in human (FIH) Phase I trial
- Convert animal dose to human dose on a mg/m² body surface area basis
- Procedure:
  - Determine NOAEL for all toxicology species
  - Determine the most sensitive species
  - Convert NOAEL in mg/kg to Human Equivalent Dose (HED)
  - Multiplication Factors:
    - Mouse = 3
    - Rat = 6
    - Monkey = 12
    - Dog = 20
    - Minipig = 35
  - Example: a 30 mg/kg dose in the monkey converts to 360 mg/m². Avg human BSA = 1.67 m². 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
  - Oncology safety factor of 1/6 the dose below that which can cause life threatening toxicities or irreversible findings
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 repro tox, carcinogenicity, host resistance studies
  - More expensive, can be harder to obtain
  - Ethical issues
Biologics – General Considerations for Toxicology Assessment

- GLP requirements for studies are the same
- Tissue cross-reactivity studies needed for monoclonal antibodies – ability to bind to target and non-target tissues
- May not be required:
  - Metabolism
  - Limited safety pharmacology
  - Genotoxicity
  - Carcinogenicity
- Highest dose in toxicology studies:
  - Scientifically reasonable multiple of the highest projected clinical dose
  - Maximum feasible dose
  - Dose reflective of a pharmacodynamic marker e.g. saturation of antigen
- Toxicity is usually due to exaggerated pharmacology
- Calculate Minimal Anticipated Biological Effect Level (MABEL)
  - From animal efficacy/PK data and \textit{in vitro} data
  - This dose may be lower than the lowest dose initially used in the clinic
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

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Cellular and Gene Therapy Products (CGT)-General Considerations for Toxicology Assessment

• Due to the species-specific nature of the clinical product, testing the human CGT product in animals may not be informative; Therefore testing of an analogous product may be a suitable alternative
• Animal species selected for assessment of bioactivity and safety should demonstrate a biological response to the investigational CGT product similar to that expected in humans
• Pilot studies essential to establish the biological relevance of a specific animal species
• Although healthy animals represent the standard model test system in traditional toxicology studies, study designs using animal models of disease/injury can supplement, or possibly be used in lieu of, toxicology studies in healthy animals
• Talk to the FDA!
Drug Scale Up and Characterization

• Increase the amount of drug that can be made in a manufacturing campaign
• Characterize it according to the regulations relevant to the phase of drug development
• A variety of physiochemical, analytical and economic factors should be considered when evaluating whether a compound should be taken into development including:
  • Clear IP protection
  • Acceptable solubility
  • Able to be formulated
  • Acceptable stability under various conditions
  • Crystal forms evaluated – are there polymorphs?
  • Analytical and bioanalytical assays developed
  • Manufacturing costs acceptable
Chemistry, Manufacturing and Controls (CMC) Issues

- Drug substance - active pharmaceutical ingredient (API)
- Drug product - API in final form with excipients

Good characterization
- Identify
- Strength
- Quality and % purity and % impurities
- Stability – identify degradation products
- Residual solvents/metals
- Packaging and storage conditions
- Require a Certificate of Analysis (COA)

Formulation
- Use safe excipients
- Formulation changes may require bridging in vivo data

Analytical/bioanalytical assay development should occur before GLP studies start
- Dose formulation analysis
- Requires validated assays

Establish stability of drug under conditions of use in GLP studies
- Expiration dating required

Manufacturing lot for GLP studies
- Adequate supply
- Impurity profile the same for nonclinical toxicology studies and clinical trials

Manufacturing changes
- Physicochemical characterization more difficult for biologics
- May need to provide bridging animal efficacy, PK and/or toxicology data
- Show bioequivalence
What Kind of Interactions and Filings Will You Have with Regulatory Agencies?

• The FDA can be approached for advice and opinions on drug development activities
• Numerous documents are available for guidance
• Specific documents are used for filing for regulatory approval to advance through clinical trials
• The initial document to enter first in human dosing is the Investigational New Drug Application (IND)
pre-IND Meeting - Information Package

• Pre-IND consultation contacts
  [link]

• 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

• Common Technical Document (CTD)
  • Detailed specifications for submissions started by the EMA and now an ICH guidance
  • Goal is to enable the use of one application for all countries
  • eCTD (electronic CTD) allows for electronic submission to regulatory agencies
  • Requires specific templates for tables of nonclinical data
• 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
Last Thoughts

- Multi-step process to identify a drug that is worthy of entering development pipeline
- Knowledge gained in Pre/Nonclinical studies will make clinical planning easier and enable better, more informative clinical trials, so don’t skimp on these studies
- It is never too early to start formulation, stability and scale up work
- Discussions with the FDA facilitate good nonclinical planning
- Ask questions!
Abbreviations

- ADME = absorption/distribution/metabolism/excretion
- PK = Pharmacokinetics
- TK = Toxicokinetics
- MTD = Maximum tolerated dose
- GLP = Good Laboratory Practices
- CMC = Chemistry manufacturing controls
- IND = Investigational New Drug application
- NOEL/NOAEL = No Observed Effect Level/No Observed Adverse Effect Level
- MABEL = Minimal Anticipated Biological Effect Level
- MRSD = Maximum Recommended Starting Dose
- NDA = New Drug Application
- BLA = Biologic License Application
- CGT = Cellular or Gene Therapy
References

- **FDA Guidances**
- **ICH 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**
- **Cellular and Gene Therapy Guidance**
- **GLPs - CRF 21 – part 58**
- **Recent reviews of P450 metabolism**
Questions?

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