Regulatory Toxicology
A Nonclinical Pharmacology and Toxicology Perspective

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The opinions expressed by Dr. Ghantous in this presentation do not reflect official support or endorsement by the Food and Drug Administration

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Presentation Overview

Regulatory Toxicology

• Overview of the Food and Drug Administration (FDA)
• Regulatory Agencies Outside of the United States
• Non-clinical Regulations and Guidance Documents
• Overview of Drug Development
• Types and Timing of Non-clinical Studies
• Overview of Clinical Trials
• Summary
Overview of FDA
FDA Mission Statement

The FDA is responsible for protecting the public health by assuring the safety, efficacy, and security of human and veterinary drugs, biological products, medical devices, our nation’s food supply, cosmetics, and products that emit radiation.
HHS/FDA

- **CDER** (Center for Drug Evaluation and Research)
- **CBER** (Center for Biologic Evaluation and Research)
- **CDRH** (Center for Devices and Radiological Health)
- **CFSAN** (Center for Food Safety and Applied Nutrition)
- **CVM** (Center for Veterinary Medicine)
- **CTP** (Center for Tobacco products)
- **NCTR** (National Center for Toxicology Research)
Human Medical Products at FDA

**CDER**
- Chemically-synthesized pharmaceuticals
- Biotechnology-derived pharmaceuticals
- (recombinant human proteins and monoclonal antibodies)
- Other (oligonucleotides, synthetic peptides, siRNA)

**CBER**
- Cell, tissue and gene therapy
- Vaccines
- Blood-derived products

**CDRH**
- Pacemakers, contact lenses, hearing aids
- Diagnostic devices, Drug delivery devices, Implants
CDER Mission Statement

• Promote and protect public health by assuring that **safe and efficacious** drugs are available to Americans

• CDER accomplishes this mission by reviewing data that sponsors submit to support the safe and efficacious use of new drugs in humans
CDER Review Divisions/OND

Office of New Drugs Immediate Office

• **Office of Drug Evaluation I**
  — Division of Cardiovascular and Renal Products
  — Division of Neurology Products
  — Division of Psychiatry Products

• **Office of Drug Evaluation II**
  — Division of Anesthesia, Analgesia and Addiction Products
  — Division of Metabolism and Endocrinology Products
  — Division of Pulmonary, Allergy, and Rheumatology Products
CDER Review Divisions/OND Cont’d

• **Office of Drug Evaluation III**
  - Division of Gastroenterology and Inborn Errors Products
  - Division of Dermatology and Dental Products
  - Division of Bone, Reproductive and Urologic Products

• **Office of Drug Evaluation IV**
  - Division of Medical Imaging Products
  - Division of Nonprescription Drug products
  - Division of Pediatric and Maternal Health

• **Office of Antimicrobial Products**
  - Division of Anti-Infective Products
  - Division of Antiviral Products
  - Division of Transplant and Ophthalmology Products
Office of Hematology and Oncology Products

- **Division of Oncology Products 1 (DOP 1)**
  Breast, Gynecologic/Supportive care, Genitourinary
- **Division of Oncology Products 2 (DOP 2)**
  Gastrointestinal, Lung/H & N, Neuro-oncology/Rare cancers/Solid Tumor Pediatric Malignancies, Melanoma/Sarcoma/reast,
- **Division of Hematology Products(DHP)**
  Benign Heme, Heme Malignancy, Heme Support
- **Division of Hematology, Oncology, Toxicology (DHOT)**
Where Does FDA Get Authority to Regulate from?

- Laws passed by congress
- CFR- Code of Federal Regulations
- Manual of Policies and Procedures (MaPPs)
- Guidance for Industry
Drug Law

• **Federal Food, Drug and Cosmetic Act of 1938**
  – Sulfanilamide and diethylene glycol

• **Drug Amendments Act of 1962**
  – Thalidomide and birth defects

  – Collect user fees to fund the new drug approval process

• **FDAMA**- Food and Drug Modernization Act of 1997
  – 6 months pediatric exclusivity
  – Fast track

• **FDAAA**- FDA Amendments Act of 2007
  – REMS- Risk Evaluation Mitigation Strategy
  – SLC- Safety Labeling Changes

• **FDASIA**- Food and Drug Administration Safety and Innovation Act of 2012
Stages of drug development

- Pre-IND
- IND
- Phase 1 clinical trials
- Phase 2 clinical trials
- Phase 3 clinical trials
- NDA
- Post-marketing
Pre-IND
Conduct non-clinical studies needed to start Phase 1
Clinical trials, prepare clinical protocol

FDA review of regulatory documents

FDA review of regulatory documents

Conduct clinical trials and non-clinical studies needed to support them

Approval
The Review Team

• Division Director, Deputy Director
• Team Leaders from each of the review teams
  – Clinical Reviewer (Medical Officer)
  – Pharmacology/Toxicology Reviewer
  – Product Quality Reviewer (CMC)
  – Clinical Virology Reviewer (in some divisions)
  – Clinical Pharmacology Reviewer
  – Statistic Reviewer
  – Regulatory Project Manager
Non-Clinical Pharmacology and Toxicology at FDA/CDER

- ~180 non-clinical pharmacology and toxicology reviewers within FDA/CDER
- Assigned among review divisions
- Each division has 1 or 2 pharmacology/toxicology supervisors and a variable numbers of reviewers
- Generally hold a PhD in pharmacology, toxicology or other life science
Types of New Products Regulated by FDA/CDER

• New entities
  – Small molecule, biologic, other
  – Not previously tested in humans
• New formulations (re-formulations) for previously tested/approved drugs
• Combinations of previously approved drugs
Testing of New Drugs for Safety and Efficacy

FDA/CDER does not test new drugs

• Sponsors and/or their contractors conduct studies (e.g., non-clinical, clinical and CMC) needed to support drug development

• Sponsors submit study reports to FDA/CDER for review

Sponsors

Pharmaceutical, biopharmaceutical companies, academic, government institutions and others
Organizations Involved in Drug Development

Food and Drug Administration (FDA)

- Sponsors
  - Pharmaceutical/biopharmaceutical companies
  - Academic institutions
  - Other

- Contract research organizations (CROs)
Pre-IND
Pre-IND

Before Submitting an IND, Sponsors…

- Define chemical properties of the drug
- Conduct nonclinical pharmacology/toxicology studies
- Develop clinical protocol(s)
Pre-IND Meetings

• Avoid premature submission of INDs
• Avoid unnecessary nonclinical studies
• Resolve potential safety issues
• Discuss the contents of the IND and overall drug development plan
• Provide regulatory guidance and answer appropriate questions
Suggested Contents of Pre-IND Briefing Packages

• Background information on the drug
• Chemical description of the drug product
• Chemistry, manufacturing, and controls
• Summaries of available nonclinical toxicology results and outlines of proposed studies
• Brief description of proposed clinical protocols and final clinical use
• List of specific questions to be discussed at the pre-IND meeting
To Maximize Benefit from a Pre-IND Meeting

• Hold the meeting early in the development process

• Submit a complete briefing package on the proposed drug product

• Submit specific questions and/or concerns regarding the nonclinical development of the drug

• Include pharmacologists and toxicologists who are involved in the nonclinical development of the drug
IND
Investigational New Drug
IND: A Request to Start Clinical Trials

• **Commercial IND** - pharmaceutical companies whose ultimate goal is to obtain marketing approval for new products

• **Investigator IND** (Research IND) – submitted by physicians who initiates and conducts an investigation

• **Single-Patient IND** – a submission that is meant to treat only one patient
IND Types Cont’d

• **Treatment IND** – experimental drugs showing promise in clinical testing for serious or life-threatening conditions
  – Criteria to meet:
    • Intended to treat a serious or life-threatening disease
    • No comparable drug or other therapy available to treat that stage of the disease in the intended population
    • Drug under investigation in a controlled clinical trial or all clinical trials have completed
    • Sponsor of the controlled clinical trial is actively pursuing marketing approval with due diligence
      – Treatment protocol submitted by an IND sponsor
      – Treatment IND submitted by a licensed practitioner (Single Patient IND) or a commercial sponsor

• **Emergency IND (EIND)**
Emergency IND (EIND)

- Emergency situation that does not allow time for submission of IND which is generally reserved for life-threatening situation in which no standard acceptable treatment is available
- IND number provided by phone
- Drug can be shipped and administered prior to submission of application to FDA
- One patient per IND
IND Review

• **21 CFR 312.22**
  - FDA’s primary objectives in reviewing an IND are, in all phases of the investigation, to assure the safety and rights of subjects and in Phase 2 and Phase 3, to help assure that the quality of the scientific evaluation of drugs is adequate to permit an evaluation of the drug’s effectiveness and safety.

• **21 CFR 312.23 (content and format)**
  - Cover Sheet (Form FDA 1571)
  - Form 3674
  - A Table of Contents
  - Introductory Statement and General Investigational Plan
  - Investigator’s Brochure
  - Protocols – a protocol for each planned study
  - Chemistry, Manufacturing and Controls Information
  - Pharmacology and Toxicology Information
  - Previous Human Experience with the Investigational Drug
  - Additional Information
Institutional Review Boards (IRBs)

- **IRB definition** – any board, committee, or other group formally designated by an institution to review, to approve the initiation of, and to conduct periodic review of, biomedical research involving human subjects. The primary purpose of such review is to assure the protection of the rights and welfare of the human subjects.

- **IRBs ensure that:**
  - Informed consents is obtained and the documents meet regulatory requirements
  - Risk to subjects are minimized
  - Risk to subjects are reasonable in relation to anticipated benefits
  - Adequate study monitoring for safety
  - Adequate protection of subject privacy
  - Rights and welfare of vulnerable subjects are protected
Informed Consent

• Obtained for every subject except where there is an exception (emergency, DOD use)
• Offered in manner to minimize possibility of coercion
• Presented in understandable language
• Contains no language that waives subject’s rights to release anyone from liability or negligence
The First 30 Days

• Study cannot proceed until 30 days from FDA receipt (new INDs and reactivated INDs only)
• 30 day safety review
• Internal meeting before the 30 days to review the application together to determine whether the proposed study is safe to proceed
• Decision: safe to proceed 😊 or clinical hold? 😞
Clinical Holds 😞

• Grounds for imposing a clinical hold differ based on phase of IND development
  – Phase 1 – Human subjects at unreasonable and significant risk, unqualified investigator, IB misleading, erroneous or incomplete, or insufficient information to assess risk
  – Phase 2 or 3 – any reasons cited above and protocol deficient in design to meet stated objective

• Can be imposed at any time

• Unless accompanied by a clinical hold, agency comments to an IND sponsor are advisory

• Partial clinical hold vs. full clinical hold
Types of Submissions to the IND

• New protocol
• Protocol amendment
• Information amendment
• Safety reports (initial and follow-up)
• Annual Reports
• Meeting request
• Special Protocol Assessment (SPA)
  – Clinical
  – Stability
  – Carcinogenicity
How Do Submissions Get to the Reviewers?

• Amendment arrives at Central Document Room (electronic or paper)
• Amendment sent to Division/Project Manager
• Amendment given to Team Leaders
• Amendment assigned to Primary Reviewers
NDA
New Drug Application
NDA: A Request to Market the Drug

NDA Consists of:

• Clinical safety and efficacy data

• Clinical pharmacokinetic data

• Nonclinical pharmacology/toxicology data

• Chemistry data

• Package labeling

• Administrative information (e.g. patent information, debarment certification)
NDA Types

- Type 1: New Molecular Entity (NME)
- Type 2: New Active Ingredient (e.g. new salt)
- Type 3: New Dosage Form
- Type 4: New Combination
- Type 5: New Formulation or New Manufacturer
- Type 6: New Indication, Same Manufacturer (no longer used)
- Type 7: Drug Already Marketed, but Without Approved NDA
- Type 8: Rx to OTC
Efficacy Supplements

• An efficacy supplement is defined based on the type of change that is being made, not the type of data the supplement contains

• The sponsor should submit a redline version of the proposed labeling so the FDA can see the proposed changes
Types of Efficacy Supplements

• New indication or a significant modification of an existing indication
• A new dosage regimen
• A new route of administration without a change of any kind of formulation for the drug product
• A comparative efficacy claim naming another drug
• A change in labeling that significantly alters the patient population to be treated
• An Rx-to-OTC switch
• Confirmatory study for Subpart H approval- accelerated approval
• Confirmatory study for Animal Rule
• A labeling supplement with clinical data
• Chemistry supplement with clinical data
• Pediatric supplement
Labeling Supplements

- Changes Being Effected (CBE)
- Prior Approval
- Division requested labeling
- Conversion to Physician’s Labeling Rule
- Safety Labeling Supplements
- Does not require a User Fee
Types of NDAs

• 505(b)(1) - applicant own or have a right of reference to all of the investigations relied upon by the application to support approval of the NDA

• 505(j) - generic application

• 505(b)(2) – an NDA that relies for approval on investigations not conducted by or for the applicant and for which the application does not have a right of reference
Type of Reviews

• **Priority review**
  Preliminary estimates indicate that the drug product, if approved, has the potential to provide:
  1. S & E therapy where there is no satisfactory alternative
  2. A significant improvement compared to marketed products,

• **Accelerated approval**
  Allows approval based on a surrogate endpoint

• **Fast-track designation**
  Designed to facilitate the development and expedite the review of new drugs intended to treat serious or life-threatening conditions (but only a serious aspect of that condition) and that demonstrate the potential to address unmet medical need (unmet need still exists if the only approvals are accelerated).

• **Rolling submission**
Breakthrough Designation

Like all of the programs directed at drugs of special importance, FDASIA’s Breakthrough designation is for drugs that may treat a serious or life-threatening condition and could represent substantial improvement over available therapy. Such drugs would of course be eligible for priority review accelerated approval, and, it seems likely anything else that Fast Track allows (rolling review).
Biologics

- **Biological Product**- “A virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein (except any chemically synthesized polypeptide), or analogous product, applicable to the prevention, treatment, or cure of a disease or condition of human beings”

- Therapeutic biological products were transferred from CBER to CDER in 2003
Therapeutic Biologic Products

- Monoclonal antibodies of *in vivo* use
- Proteins intended for therapeutic use that are extracted from plants, animals or microorganisms, including recombinant versions
- Cytokines, growth factors, enzymes, immunomodulators and thrombolytics
- Other non-vaccine therapeutic immunotherapies
Current Biologic Laws

• Public Health Service Act (1994)
  – Section 351- Licensure of biological establishments and products

  – Which interprets that “biological products” are also “drugs”

• Patient Protection and Affordable Care Act
  – Biologics Price Competition and Innovations Act of 2009
Unique to Biologics

• At the time of first approval of a biological product, the Applicant is issued a four digit U.S. License Number
• There is only one U.S. License Number issued to an Applicant and it must be listed on all carton, container, and package labels
• Cooperative manufacturing arrangements are permitted but the Applicant must be listed as the manufacturer on all labels
• When a biological product is withdrawn from the market, the biologics license to manufacture that product will be revoked
How Does a Biologic License Get Approved?

• The secretary shall approve a biologics license application:
  – On the basis of a demonstration that
    • Product is safe, pure and potent
    • The facility(ies) meet standards designed to assure that it continues to be safe, pure, and potent
21st Century Review
21st Century Review

• Receive electronic submission from the sponsor. The submission is date stamped in the document room.
• Ensure conformance to regulatory requirements
• Establish review team and distribute submission
• Acknowledge receipt of submission by day 14
21st Century Review: Planning the Review

- Hold filing and planning meeting (Day 45)
- Inform applicant of a review clock (Day 60)
  - Priority (6 months) vs. Standard (10 months)
- Notify applicant of refuse-to-file determination (Day 60)
- Advisory Committee meeting required?
- Finalize sites for inspection
- Send consults to other divisions (OPDP, OSE..etc.)
- Conduct review and have monthly meetings (filing meeting, midcycle, labeling meeting, wrap up meetings, REMS, PMC/PMR)
- Official Action (Complete Response or Approval)
- Post marketing
21st Century Review: PDUFA V
“The Program”

- Applies to all NME NDAs and original BLAs (fiscal years 2013 – 2017)
- Same 21st century review timeline with modifications
  - Additional two months added on to the review period (Priority 6 months = 8 months, standard 10 months = 12 months)
  - More frequent communication with the applicant
    - Mid-Cycle Communication Teleconference
    - Late-Cycle Meeting with the applicant
User Fee


- User fee is required to submit clinical information to the FDA for review (NDA, BLA, sNDA and sBLA)

- Fees (Fiscal Year 2014):
  - Original application: $2,169,100
  - Supplemental application: $1,084,550
Formal Meetings: Types

- **Type A**: stalled development (e.g., clinical hold, dispute resolution, special protocol)
- **Type B**:
  - Pre-INDs
  - End of Phase 1 (EOP1)
  - End of Phase 2 (EOP2)
  - Pre-NDA/Pre-BLA
- **Type C**: all others

Face to face vs. teleconference

Written response only

Only Pre-IND or Type C meetings
Timeline for Meetings

• **Type A meeting**
  – Scheduled within 30 days of meeting request
  – Package due at least 2 weeks before the formal meeting

• **Type B meeting**
  – Scheduled with 60 days of meeting request
  – Package due at least 4 weeks before formal meeting

• **Type C meeting**
  – Scheduled within 75 days of meeting request
  – Package due at least 4 weeks before formal meeting
Regulatory Agencies Outside of the United States
Europe

• European Medicines Agency (EMA)
  – Decentralised body of the European Union with headquarters in London
  – Evaluates and supervises medicines for human and veterinary use
  – Scientifically evaluates marketing authorisations for medicinal products
  – Scientific work conducted by committees
Europe

EMA Committees
– Committee for Medicinal Products for Human Use (CHMP)
– Committee for Medicinal Products for Veterinary Use (CVMP)
– Committee for Orphan Medicinal Products (COMP)
– Committee on Herbal Medicinal Products (HMPC)
– Paediatric Committee (PDCO)
– Committee for Advanced Therapeutics (CAT)
United Kingdom

Medicines and Healthcare Products Regulatory Agency (MHRA)

– Assesses safety, quality and efficacy of medicines for human use
– Oversees audit of medical devices
– Operates post-marketing surveillance for adverse events
– Regulates clinical trials for medicines and medical devices
Japan

Pharmaceutical and Medical Devices Agency (PMDA)
– Established in April 2004
– Provides relief services to those suffering from adverse drug effects, infections from biological products and others
– Conduct approval reviews for pharmaceuticals and devices, provide guidance and advice relating to clinical trials and other related functions
– Ensure post-marketing safety
Non-Clinical Regulations and Guidance Documents
What are Regulations and Guidance?

- **Regulations**
  - Provide plans for following/enforcing laws
  - Legally binding
  - Defined in Code of Federal Regulations (CFR)

- **Guidance**
  - Provides direction and a course of action
  - Not legally binding
Regulations

Code of Federal Regulations

http://www.gpoaccess.gov/CFR/INDEX.HTML
Examples of Regulations

• 21CFR58
Good Laboratory Practice for Non-clinical Laboratory Studies

• 21CFR312
Investigational New Drug Application

• 21CFR314
Applications for FDA Approval to Market a New Drug
Good Laboratory Practice
21 CFR 58
CFR - Code of Federal Regulations Title 21

This database includes:
- a codification of the general and permanent rules published in the Federal Register by the Executive departments and agencies of the Federal Government. Title 21 of the CFR is reserved for rules of the Food and Drug Administration. This database contains content that is current as of April 1, 2013. For a daily compilation of CFR and Federal Register amendments, see the Electronic Code of Federal Regulations.

Search Database

Title 21 Part Section (e.g., 862.1365) | Full Text Search

Search Results:
(1) General enforcement regulations

Other Databases
- 510(k)s
- Adverse Events (MAUDE)
- CDRH 501A Electronic Reading Room
- CLIA
- Device Classification
- Inspections
- Medsun Reports
- Premarket Approvals (PMAs)
- Post-Approval Studies
- Postmarket Surveillance Studies
- Radiation-Emitting Products
- Radiation-Emitting Electronic Products Corrective Actions
- Recalls
Good Laboratory Practice
A Historical Perspective

• Until mid 1970s FDA assumed that study reports accurately described study conduct and precisely reported study data

• In 1974 – 1975, FDA reviewed facilities and found serious deficiencies

• Good Laboratory Practice (GLP) regulations developed to ensure quality of data and studies
Good Laboratory Practice

- Prescribes good laboratory practices for conducting nonclinical laboratory studies that support or are intended to support applications for research of marketing permits for products regulated by the Food and Drug Administration.”

- Does not apply to “basic exploratory studies carried out to determine if a test article has any potential utility or to determine physical or chemical characteristic of a test article”.

[Code of Federal Regulations, Title 21, Part 58, Good Laboratory Practice for Nonclinical Laboratory Studies]
Good Laboratory Practice

• GLP

• Scope
  – Organization and personnel
  – Facilities
  – Equipment
  – Testing facility operation
  – Test and control articles
  – Protocol
  – Records and report
Guidance Documents

• International Conference on Harmonization
• (ICH)
• FDA/CDER
Why are there Guidance Documents?

• 21 CFR 312 – Pharmacology and toxicology
  – “Adequate information about pharmacological and toxicological studies of the drug involving laboratory animals or in vitro, on the basis of which the sponsor has concluded that it is reasonably safe to conduct the proposed clinical investigations. The kind, duration, and scope of animal and other tests required varies with the duration and scope of the proposed clinical investigations. Guidance documents are available from FDA that describe ways in which these requirements may be met.”
The ICH Process

Established in 1990 to improve efficiency of the new drug approval process in Europe, Japan and the United States

• Regulators and industry representatives from all 3 regions participate
• Harmonized topics are safety, quality, efficacy and multidisciplinary
Where to find guidances?

- http://www.fda.gov/
Overview of Drug Development

Diagram showing the stages of drug development:
- Discovery
- Clinical
- Non-clinical/Preclinical
- Phase 1, 2, and 3 Clinical Trials
- Phase 4 Clinical Trials
- Pre IND
- IND
- NDA/BLA APPROVAL
Drug Development 101

- **Pre-Clinical Research**
  - Synthesis and Purification
  - Animal Testing
  - Short-Term
  - Long-Term
  - Institutional Review Boards

- **Clinical Studies**
  - Phase 1
  - Phase 2
  - Phase 3
  - Accelerated Development Review
  - Treatment IND

- **NDA Review**
  - FDA Time
  - Industry Time
  - Sponsored/FDA Meeting Encouraged
  - Advisory Committees
  - IND Submitted
  - Early Access: Subpart E
  - NDA Submitted
  - Review Decision
  - Sponsor Answers Any Questions from Review
Chemistry, Manufacturing and Controls

- CMC
  - Address discipline specific scientific and regulatory concerns to ensure that the manufacturing and control processes result in safe drugs being produced for clinical trials and marketing
Non-Clinical Perspectives

Non-clinical studies are conducted to support clinical trials and, ultimately, approval for new drugs.
Types and Timing of Non-Clinical Studies
How do Non-Clinical and Clinical Development Influence Each Other?

• How do you get from non-clinical studies into the clinic?
• What types of non-clinical studies are needed to continue clinical development?
• What role do non-clinical studies play in clinical trial design?
Non clinical studies M3(R2)

- Safety pharmacology
- Pharmacokinetics
- ADME (absorption, distribution, metabolism, elimination)
- General toxicology
- Local Tolerance
- Genotoxicity
- Carcinogenicity
- Reproductive toxicology
- Special studies
Exceptions

• ICH M3’s recommendations for types and timing of studies most directly applicable to systemically-administered small molecules intended to treat non-life-threatening conditions

• Exceptions
  – Life-threatening conditions
  – Topically-applied products (skin and eyes)
  – Certain medical imaging agents
  – Biologics
# Types and Timing of Non-clinical Studies

<table>
<thead>
<tr>
<th>Study Type</th>
<th>Timing (Relative to Clinical Trials)</th>
<th>Small Molecule</th>
<th>Biologic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharmacodynamics</td>
<td>Prior to Phase 1</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td><em>In vitro</em> metabolic profile and plasma protein binding</td>
<td>Prior to Phase 1</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Systemic exposure</td>
<td>Prior to Phase 1</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Comparative <em>in vivo</em> animal and human metabolism data</td>
<td>Generally prior to Phase 3</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

*Reflects ICH M3(R2), 2009*
# Types and Timing of Non-clinical Studies

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<th>(Relative to Clinical Trials)</th>
<th>Small Molecule</th>
<th>Biologic</th>
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</thead>
<tbody>
<tr>
<td>Safety pharmacology</td>
<td>Prior to Phase 1</td>
<td>Yes</td>
<td>Product specific</td>
</tr>
<tr>
<td>- Cardiovascular</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Respiratory</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>- CNS</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>General toxicology</td>
<td>Prior to Phase 1, 2 and 3</td>
<td>Yes (2 species)</td>
<td>Yes (1 species acceptable)</td>
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<th>Timing (Relative to Clinical Trials)</th>
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<tbody>
<tr>
<td>Genotoxicity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Bacterial mutation</td>
<td>• Prior to Phase 1</td>
<td>Yes</td>
<td>Generally no</td>
</tr>
<tr>
<td>• <em>In vitro</em> chromosomal aberrations</td>
<td>• Prior to Phase 1</td>
<td></td>
<td></td>
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<tr>
<td>• <em>In vivo</em> chromosomal aberrations</td>
<td>• Prior to Phase 2</td>
<td></td>
<td></td>
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<tr>
<td>• <em>In vivo</em> micro nucleus</td>
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<th>Small Molecule</th>
<th>Biologic</th>
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</thead>
<tbody>
<tr>
<td>Reproductive Toxicology</td>
<td>• Prior to Phase 3&lt;br&gt;• Prior to Phase 3&lt;br&gt;• Prior to Phase 3&lt;br&gt;• Marketing approval</td>
<td>Generally Yes</td>
<td>Product specific</td>
</tr>
<tr>
<td>• Embryo-fetal development</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Male fertility</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Female fertility</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Pre-/post-natal development</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carcinogenicity</td>
<td>Marketing approval</td>
<td>Yes (chronic drugs)</td>
<td>Product specific</td>
</tr>
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## Nonclinical Programs for Small Molecules

<table>
<thead>
<tr>
<th>Study Type</th>
<th>Oral</th>
<th>Dermal</th>
<th>Ocular</th>
</tr>
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<tbody>
<tr>
<td>General toxicology</td>
<td>Rat and dog</td>
<td>Mini-pig (dermal) Rat (systemic)</td>
<td>Rabbit, pig, dog, monkey (ocular) Rat/non-rodent (systemic)</td>
</tr>
<tr>
<td>Genotoxicity</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Safety Pharmacology</td>
<td>Yes</td>
<td>Generally yes, but consider systemic exposure and body surface area</td>
<td>Not routinely expected</td>
</tr>
<tr>
<td>Melanin Binding</td>
<td>Not routinely</td>
<td>Not routinely</td>
<td>Generally yes</td>
</tr>
<tr>
<td>Photosafety</td>
<td>As needed</td>
<td>As needed</td>
<td>As needed</td>
</tr>
<tr>
<td>Hypersensitivity</td>
<td>Not routinely</td>
<td>Yes</td>
<td>Not routinely</td>
</tr>
<tr>
<td>Reproductive toxicology</td>
<td>Yes</td>
<td>Yes</td>
<td>Might be able to waive some studies</td>
</tr>
<tr>
<td>Carcinogenicity</td>
<td>Yes</td>
<td>Yes</td>
<td>Might be able to waive</td>
</tr>
</tbody>
</table>
What is the Role of Non-Clinical Studies?

- Data from non-clinical studies are used to support the safety of clinical trials and drug approval
  - Identify adverse effects of a drug
  - Select starting dose for Phase 1 clinical trials
  - Support safety of ongoing clinical trials
Questions that Non-Clinical Studies Answer

• What are the toxic doses in animals?
• What are the target organs?
• How do the toxic doses compare to the effective/clinical dose(s)?
• Can the toxicities be monitored in patients in the clinical trials?
• Are the toxicities reversible?
Non-Clinical Reasons for Clinical Hold

- Appropriate studies were not conducted
- Study designs were flawed
  - Insufficient number of animals
  - Inappropriate endpoints
  - Study duration not appropriate
- The toxicities presented unacceptable risk
- NOAEL was not identified
Overview of Clinical Trials
Phase 1, 2, and 3 Trials

**Phase 1:**
- Safety and pharmacokinetics
- Generally 20 to ~80 subjects
- Closely controlled

**Phase 2:**
- Efficacy and safety
- Usually no more than several hundred subjects
- Closely controlled

**Phase 3:**
- Efficacy and safety
- Several hundred to several thousand subjects
Clinical Trials

- Phases of clinical investigation defined in 21 CFR 312.21
- IND may be submitted for one or more phases of an investigation
- Clinical investigation of a new drug is generally divided into 3 phases
  - Phases 1, 2 and 3
Clinical Trials

• Phase 1 Clinical Trials
  – Includes initial introduction of a new drug into humans
  – Closely monitored
  – Safety and pharmacokinetics, drug metabolism and mechanism of action
  – Healthy volunteers or patients
  – Generally 20 to 80 subjects
Clinical Trials

Phase 2 Clinical Trials

– Evaluate effectiveness of a new drug for a particular indication in patients with the disease
– Define doses for Phase 3
– Determine short-term risks and side effects
– Closely monitored
– No more than several hundred subject
Clinical Trials

Phase 3 Clinical Trials

– Performed after preliminary evidence of efficacy has been demonstrated
– Intended to gather additional information on safety and efficacy
– Evaluate risk vs. benefit
– Several hundred to several thousand subjects
What are Phase 1a, 1b, 2a and 2b?

- No regulatory definition or description
- Way to classify/subdivide clinical trials
- Example
  - Phase 1a – Single dose
  - Phase 1b – Repeat dose
What is Phase 0?

Exploratory IND (eIND) approach

– Limited human exposure
– No therapeutic intent
– Not intended to examine tolerability
• Non-clinical approach more limited than for traditional IND
– Different options possible
• Most applicable to imaging agents
What is Phase 0?

eIND guidance documents

Types of action

• Approval
• Complete Response (CR)
  – Results of studies (non-clinical and/or clinical) show that drug is unsafe for use under the proposed conditions
  – Lack of evidence of efficacy
  – Chemistry and manufacturing issue
Package Insert / Labeling

Printed information providing directions for use and adequate warnings

- Contains non-clinical, clinical and chemistry information

- FDA and sponsors negotiate content
Package Insert / Labeling

Pharmacology/Toxicology part of labeling:

• Carcinogenesis, Mutagenesis, Impairment of Fertility

• Pregnancy Category (no more)

• Animal Pharmacology and/or Animal Toxicology
Advice for Interacting with FDA

• Follow procedures defined in Formal Meetings with Sponsors and Applicants for PDUFA Products (2000)

• For interactions not covered by the above, contact FDA Program Manager assigned to the submission in question
Questions???
Please click on the link below to enter your comments on this talk

https://www.surveymonkey.com/s/VNZC9MQ