FROM DISCOVERY TO COMMERCIALIZATION

At least 10 years on average

Average spend of $1.4B

Less than 12% of drugs entering Phase I are approved
DRUG DEVELOPMENT – MAJOR STEPS

Discovery

Preclinical Research
- API synthesis
- Analytical methods
- Animal testing
- Formulation

Pre-IND meeting with FDA

Clinical Research
- Phase I
- Phase II
- Phase III

End of Phase II meeting with FDA

FDA Review/Approval

Pre-NDA/BLA meeting with FDA

Post-Market Surveillance

Valley of Death
DISCOVERY PHASE

Target Identification and Validation
Assay Development
High-Throughput Screening
Medicinal Chemistry
In Vitro Efficacy, Biological Screening Assays
Animal Efficacy Models
Lead Optimization (Potency, Bioavailability)
PRE-IND STRATEGIES AND GOALS

Chemical Development Strategies
• Robust API synthetic route
• Clinically suitable drug formulations
• Well characterized impurity profiles

IND-Enabling Pharmacology, DMPK & Toxicology studies
• Align with clinical trial plans
  ▪ Route of administration
  ▪ Dose schedules
  ▪ Duration of treatment
• PK/PD responses
• Target organs
• Dose response
• Exposure multiples
• Safety margins
DRUG DEVELOPMENT INTEGRATES MANY FIELDS

In Vitro ADME
- Log D, Solubility
- Cytotoxicity
- Protein binding
- Permeability
- Metabolism
- CYP Assays

DMPK
- Bioanalytical method development and validation
- Bioanalytical sample analysis
- PK & metabolite profiling

Preclinical Development
- Pharmacology
- Metabolism studies
- Animal models
- Pharmacokinetics
- Toxicology (IND & beyond)

Chemical Services
- cGMP synthesis (grams to kilos)
- Process chemistry
- Analytical chemistry
- Process development & engineering

Clinical & Regulatory Support
- Clinical Sciences
- Ph 1 PK/Safety
- Ph 2 Efficacy designs
- Regulatory strategies & submissions
REGULATIONS
DRUG DEVELOPMENT AND THE FDA

Code of Federal Regulations (CFR)

Good Laboratories Practices (GLP): 21 CFR 58

Good Manufacturing Practices (GMP): 21 CFR 211

Biologic Products 21 CFR 600

Viral Vaccines 21 CFR 630
GOOD LABORATORY PRACTICES (GLP)

Quality system for execution of non-clinical safety studies

Ensures data integrity for FDA making risk/safety assessments

Definitive preclinical studies must be GLP compliant

Personnel, Facility, Documents, Test and Control Articles
GOOD MANUFACTURING PRACTICES (GMP)

Quality assurance for consistent product manufacturing

Controls for quality standard appropriate to developmental stage of drug

Identity, Safety, Purity, Efficacy, Potency, Stability, Consistency
PRIOR TO INITIATION OF ANIMAL STUDIES

Manufacture of test article

Development of analytical and bioanalytical methods

Preformulation studies

Development of appropriate dosing formulations
GMP STUDIES
CHEMISTRY, MANUFACTURING, AND CONTROLS (CMC)

Chemistry
- Description and characterization
- Specifications (tests, methods, acceptance criteria)
- Analytical Methods (chemical structure and activity, excipients, purity and stability)
- Reference Standard
- Certificate of Analysis
- Purity profile
- Formulation development

Drug Substance
New Chemical Entity (NCE), Test Article, Active Pharmaceutical Ingredient (API)

Drug Product
Formulated Drug, including container and packaging
Manufacturing

- Well-defined, controlled manufacturing process
- GMP compliant
- Qualified manufacturer
- Synthesis/method of manufacture
- Purification
- Scale up
- GMP production
- Formulation
- Release testing
- Stability of drug substance and drug product
- Packaging and Labeling
  - Container/closure system for drug substance storage
  - Container/closure system for drug product shelf life
- Distribution
Quality System (Controls), includes

- Quality Control, Quality Assurance
- Raw Materials Controls
- Production and Process Controls
- Complaints
- Qualified Vendors
- Design and performance-based specifications
- Continuous improvement
- Risk assessment
NON-GLP STUDIES
EARLY DEVELOPMENT, IN VITRO METABOLISM

Critical for Non-clinical Species Selection & Prediction of Human DMPK Responses

In Vitro Metabolism

- Plasma stability
- Protein binding
- Metabolism (microsomes, hepatocytes)
- Species comparison in microsomes & hepatocytes
- Define metabolic pathway and major metabolites; metabolite structure elucidation
Cytochrome P450 CYP Assays, Inhibition and Induction
• Family of enzymes with major role in the metabolism of drugs
• May affect plasma levels in vivo and potentially lead to adverse drug reactions or toxicity

UGT Enzyme Inhibition
• Family of enzymes with major role in the metabolism of drugs (Phase II)
• Major role in drug clearance

Drug Transport (absorption, permeability, active transport)
• Permeability, to predict human intestinal permeability
  ▪ Caco2, PAMPA, MDR1-MDCK (P-gp)
• Uptake transporter assays

EARLY DEVELOPMENT, DRUG-DRUG INTERACTIONS
Critical for predicting Drug-Drug Interactions, interpreting PK & Tox outcomes, prediction of human PK profiles
Pharmacokinetics (PK)

- Lead & Formulation selection, pilot PK
- Bioavailability
- Define Active Drug Concentration & PK profiles (major & relevant metabolites)
- AUC, Cmax/Cmin, Tmax, T1/2, Vd, & Cl
- Characterize over range of dosages, including expected clinical and toxicology dosages (1x-10x efficacious dosages)
- Single & Repeat-dose PK (3-7 days)

Defines saturation of absorption, metabolism, clearance/excretion, accumulation, gender and species differences
GLP STUDIES
VALIDATED METHODS FOR GLP ANIMAL STUDIES

Dose Formulation Analysis Development and Validation
Bioanalytical Method Development and Validation

Small molecules - LC/MS/MS
Biologics - ELISA

- 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
GLP vs non-GLP
- Any study can be conducted in accordance with GLP
- GLP incurs increased cost and timelines
- GLP (only) required for extrapolation to humans

Species Selection
- Selection based on in vitro metabolism and PK data
- Major metabolites must be expressed in tox species
- Rodent (mice, rats)
- Non-Rodent (dogs, nonhuman primates)
  - Gottingen mini-pigs, rabbits, etc. as justified
- Requirement for two species may be waived (ex. no pharmacology in rodent species for biologics)
Dose Administration & Schedule
should be the same as intended clinical route & schedule

Dose schedule: daily (or multiple daily) vs. cycle dosing
- **Oral**: gavage, nasogastric route, oral tablet/capsule or solution
- **Parenteral**: intravenous, continuous intravenous infusion, subcutaneous, intramuscular, intraperitoneal
- **Topical**: dermal, ocular
- **Regional treatment**: intra-tendon, intra-articular, intra-vitreal

Characterize dose-response relationship
- Minimum of 3 dosages
- Good separation between dosages to avoid exposure overlap
- Dose to toxic effect or maximum feasible limit
• Initial toxicity readouts (single and multiple dose)
• Required in each species, non-GLP
• **Tolerability** - define the Maximum Tolerated Dose (MTD): single dose; morbidity/mortality, GI distress, severe CNS effects, respiratory distress, immune reactions
• **Repeat Dose Range-Finding Toxicity**: repeat dose 5-14 days; identify dose & exposure responses, target organ toxicity; major organ system pathology; dose-limiting toxicities; repeat-dose TK
• A go/no-go decision often follows: Toxicity profile? PK profile? Dose limitations? Off target tox?

**PILOT TOXICOLOGY STUDIES**

Need complete and robust pilot studies
Consider formulations carefully
IND-ENABLING (PIVOTAL) TOX STUDIES: GLP

2 species, rodent and non-rodent (biologic may only need 1 species)

Typically 14-28 day repeat dose to support SAD & MAD Phase 1 clinical studies

Dose selection intended to elicit toxicity

Primary endpoints are clinical pathology & anatomical pathology assessments with TK profile correlates. Expected to include endpoints relevant to molecular class, anticipated toxicity, PD identification

Goals: Identify target organ toxicity/pathology, translational predictive safety biomarkers, assess reversibility or progression, assess local tolerance, determine adverse effects with NOAEL & exposure ratios

Basis for selecting initial clinical doses & escalation
IND-ENABLING TOX STUDIES

Specific assessments as indicated

• Local effects (ex. injection or application site)
• Specific safety biomarkers as appropriate (clinical pathology or specialty assay)
• Immunogenicity as warranted (anti-drug antibody)
• Immune suppression or cytokine storm

Common concerns / issues

• Blood volume limitations
• Test Article consumption substantial for large animals
• Maintain purity of purpose = IND enabling. Avoid discovery investigations; pitfall for including unneeded endpoints
ADDITIONAL GLP STUDIES NEEDED FOR THE IND SUBMISSION
GENOTOXICITY (DNA DAMAGE)

Minimum prior to Single Dose Study
   Ames Test for mutations

Minimum Prior to Multiple Dose Study:
   Chromosomal Abnormalities, in vitro (e.g., mouse lymphoma)

Prior to Phase 2 :
   Chromosomal Abnormalities, in vivo (mouse micronucleus)

Consider conducting all 3 assays pre-IND
ICH Core Battery
• Cardiovascular (generally canine or non-human primate)
• Respiratory (generally rat)
• CNS (generally rat)

Supplementary
• GI, Renal, others as target organs dictate

Purpose and Designs
• Determine potential for untoward pharmacology
• Single dose pharmacology study, top dose near Maximum Tolerated Dose (MTD)
• Small molecule, commonly stand alone studies
• Biologic, incorporate endpoints into non-rodent tox study
• Oncology (end stage), waived
SAFETY PHARMACOLOGY, ICH CORE BATTERY

Cardiovascular Assessments
- In vitro hERG (minimum, other ion channel assay as indicated)
- In vivo telemetry cardiovascular functional evaluations: blood pressure, heart rate, and ECG waveform analyses

Respiratory Functional Assessments
- In vivo respiratory assessment in rodents
- Plethysmography measuring respiratory rate, tidal volume, and minute volume

CNS Functional Assessments
- In vivo central nervous system functional assessment in rodents
- Functional observational battery (Irwin Test)
- Motor & behavioral activity
TYPICAL TIMELINES
CMC DEVELOPMENT TIMELINE

Small Molecule (8 - 12 months)
- Synthetic process improvement & production of small batches
- Chemical synthesis process development for pilot batch
- API characterization and stability established
- Initial non-clinical & clinical formulations developed
- Drug product characterization supporting early clinical use

Biologic (12 - 24 months)
- Cell line development and evaluation
- Generation of MCB
- Process development
- Demonstration run
- Analytical and Formulation
- cGMP drug substance
- Viral clearance
- Drug product release and stability testing
TOXICOLOGY DEVELOPMENT TIMELINE

Non-clinical pre-IND studies (typical 8 - 12 months)

- In vitro DMPK studies
- Pilot pharmacokinetic & toxicology studies
- Drug safety IND-enabling toxicity studies (14 - 28 day rodent and non-rodent)
- Genotoxicity assays
- Safety pharmacology profile
Manufacturing (made in cells, bacterial or mammalian)
- 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
- Viral clearance

Animal Safety Studies, special concerns
- Perform tissue cross-reactivity studies for antibody drugs
- Immunogenicity, development of anti-drug antibodies
- Animals not necessarily predictive of humans
- Non-human primate (NHP) such as cynomolgus or rhesus monkeys often used
- Highest dose often is maximum feasible dose
IND (INVESTIGATIONAL NEW DRUG) SUBMISSION PROCESS
21 CFR 312.82

Objectives

Review and reach agreement on the design of animal studies needed to initiate human testing

Discuss the scope and design of Phase 1 testing

Discuss the best approach for presentation and formatting of data in the IND
IND FILING WITH FDA, LOGISTICS

Request for meeting is made in writing

Request includes

- Product description
- Description of clinical indication and approach
- Identification of purpose of meeting, objectives and draft of specific questions
- Suggested dates / times for the meeting

FDA will respond within 14 days of receipt of request

FDA will schedule the meeting within 60 days of request receipt
PRE-IND MEETING WITH FDA, WHAT TO SUBMIT

Pre-IND package (submit 4 weeks prior to the scheduled meeting)

- Product name and chemical structure
- Proposed indication
- Preclinical data and planned studies
- Manufacturing scheme
- Product characterization data, proposed specifications
- Rationale for safety, based on toxicological profile and safety margin using dose regimen and exposure
- Draft clinical protocol
- Specific questions grouped by discipline (CMC, preclinical, clinical)

Meeting is typically held by phone and is scheduled for 60 minutes

FDA will send formal meeting minutes within 30 days after the meeting takes place
FDA has identified the following recurrent problems at pre-IND meetings:

- Inadequate CMC information
- Insufficient pre-clinical support
- Unacceptable clinical trial design
- Noncompliance with Good Clinical Practices (GCPs)
- Lack of information on selection of dosage
IND FILING WITH FDA

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
TRANSLATION GAP – KEEP INNOVATING!

NIH grants by degree of PI

Pharma spending and output

Source: NIH, CMR International & IMS Health
Heidi Nelson-Keherly, PhD
Executive Director, Preclinical

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ADDITIONAL FDA MEETINGS DURING IND CYCLE

End of Phase 1

End of Phase 2 / Pre-Phase 3

Pre-BLA (Biologics Licensing Application)
STUDIES TO COMPLETE PRIOR TO NDA/BLA SUBMISSION

GLP STUDIES

DART (developmental and reproductive tox)
  Segment I (fertility)
  Segment II (rat/rabbit teratogenicity)

Other, as appropriate
  Immunotoxicity
  Phototoxicity
  Abuse liability
  Impurity tox
  Degradant tox
GLP STUDIES

ADME (absorption, distribution, metabolism and excretion)
  • Radiolabel mass balance and tissue distribution studies
    Tissue half-life
    Clearance rates
    Potential sites of toxicity after systemic exposure

Chronic Toxicology in 2 species for repeat dosing
  Rodent, 6 months
  Non-rodent, 9 months

Carcinogenicity (rat / mouse)

DART (developmental and reproductive tox)
  Segment III (prenatal, postnatal)
## Recommended Chronic Tox Study Length

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<th>Duration of Indicated Treatment</th>
<th>Rodent</th>
<th>Nonrodent</th>
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