
Preclinical Development of Drugs for Alzheimer's Disease

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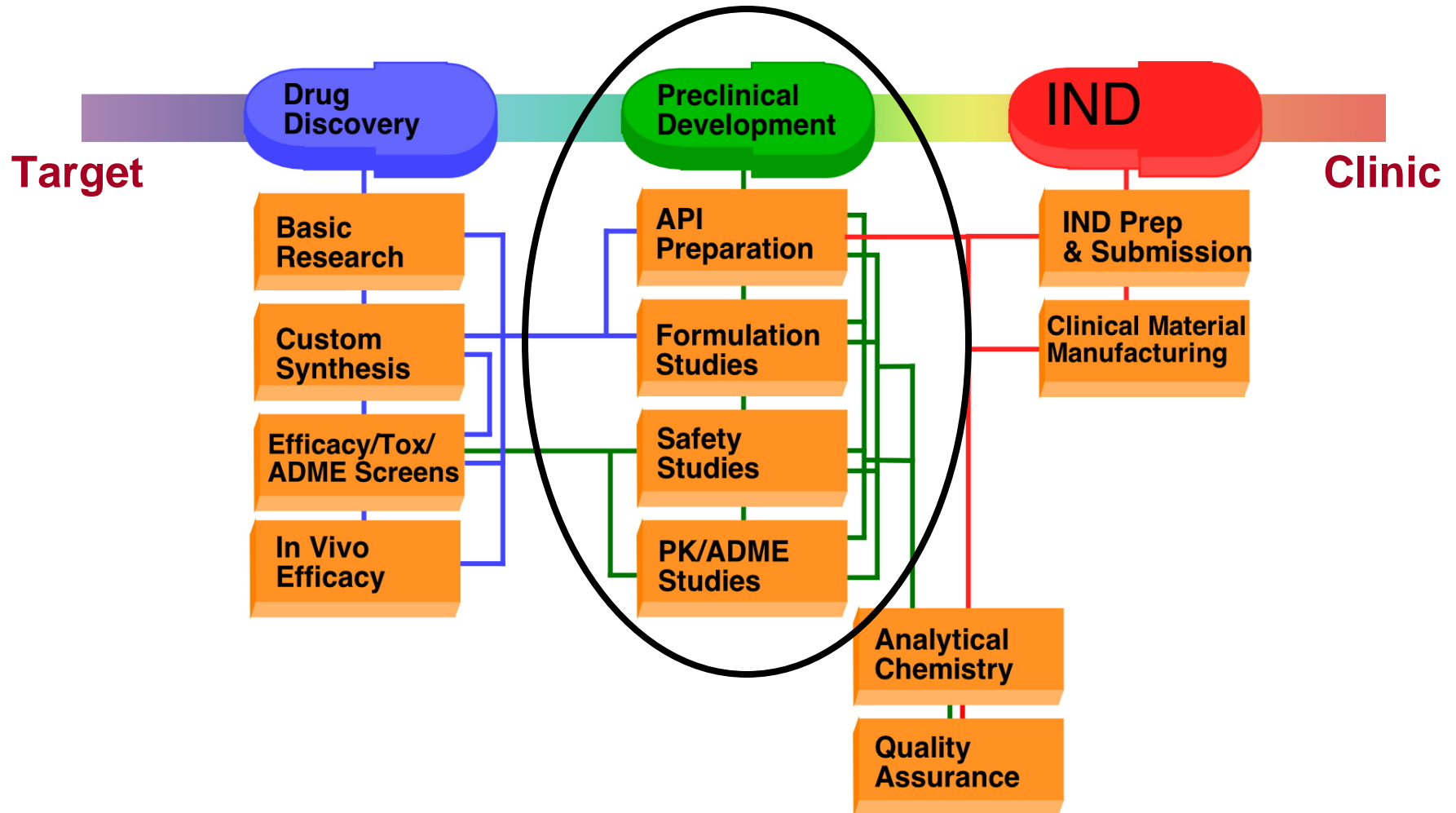
Overview

- **What is Preclinical Development?**
- **ADME / Pharmacokinetic studies**
- **Toxicology studies**
 - Dose range finding and MTD
 - Definitive GLP studies
- **Safety Pharmacology studies**
- **Genetic Toxicology**
- **API, Formulation and GMP Manufacturing**
- **Regulatory Support**



From Idea to IND

...from the lab to the clinic



API = Active Pharmaceutical Ingredient



Know where you are going...

...Patient Profile

- **Elderly**

- Low concern for pregnancy, unlikely to develop new cancers
- Altered metabolism, immune system, etc.
 - Note: young animals are preferred test system

- **Potential for drug-drug interactions**

- **Physical impairment**

- Difficulty / inability to swallow large capsules or tablets

- **Cognitive impairment**

- Potential dosing non compliance
- Need to reduce dosing complexity by integration with routine activities (e.g. bedtime, meals)



Know where you are going...

...the Drug Profile determines the testing strategy

- **NCE / NME Category**

- small molecule, peptide/protein, antibody, RNAi, DNA

- **Diagnostics (e.g. radiolabeled imaging agents)**

- Infrequent very low “microdose”
- Usually intravenous

- **Vaccine**

- Single or limited/minimal course of treatment
- Non/low affected individuals
- Usually subcutaneous/intradermal or intramuscular

- **Chronic treatment**

- Multiple dose and long-term exposure (treatment for months or years)
- Various possible routes (oral, dermal, nasal)



NCE = new chemical entity, NME = new molecular entity



Testing Strategy Overview

example: small molecule

- **GLP Range-finding Studies (non GLP)**
- **Bioavailability (BA), Pharmacokinetics (PK), Metabolism**
- **Definitive Repeated Dose Toxicity Studies (GLP)**
- **Safety Pharmacology (GLP)**
- **Genetic Toxicology (GLP)**
- **Ancillary Studies**
 - Follow up to understand specific toxicity or species differences
 - Assays specific to intended clinical use



Non GLP Studies

Toxicity screens



- **Dose range-finding escalation or reduction**
 - *Rodent and non rodent (rat and dog or rabbit or non human primate)*
 - *Very small group sizes (e.g. 1/gender/dose level, no control)*
 - *Single dose by intended route (e.g. oral)*
 - *Dose, observe for 3 days, dose up/down depending upon severity of clinical signs*
 - *Minimal number of endpoints: Clinical Observations*

- **Dose range-finding and Maximum Tolerated Dose (MTD)**
 - *Rodent and non rodent (rat and dog or rabbit or non human primate)*
 - *Single and multiple dose regimens by intended route (e.g. oral)*
 - *Daily observations following conclusion of dosing (e.g. 14 days)*
 - *May be non terminal (e.g. dogs)*
 - *Minimal number of endpoints: Clinical Observations and Clin Path*



Bioavailability and Pharmacokinetics (BAPK)

...where did it go?

- **Bioanalytical Method Development and Validation**
 - Quantify drug and/or metabolites in biological matrices (usually plasma)
- **Bioavailability (BA)**
 - Single dose, IV and intended route (e.g. oral)
 - AUC comparisons between IV administration and intended route
- **Pharmacokinetics (PK)**
 - Rodent and non rodent (usually same as MTD studies)
 - Drug availability by intended route, mean residence time, half-life
- *• **Blood Brain Barrier (BBB) Bioavailability**
 - Measure drug accumulation in the brain
 - Fraction of circulating levels to brain levels



Metabolic Profile

- **Comparative Metabolism**

- *Important when interspecies differences are observed*
- *Hepatic microsomes and cytosolic fractions from different species*
 - *Human, mouse, rat, rabbit, dog, non human primate, guinea pig, etc*
 - *Time-course loss of parent compound*
- *Metabolite identification*

- **Metabolic Inhibition**

- *Identify potential for Drug-Drug interaction*



Definitive GLP Studies (GLP)

IND-Directed Repeated Dose Toxicity Studies

- **Rodent and non rodent** – selected from range-finding studies
- **4 Dose Groups: Control (vehicle), Test Article (low, mid, high)**
- **Dosing usually by intended route and approximate frequency**
 - 3 times weekly for 4 weeks (for intermittent clinical administration)
 - Daily oral dosing for 28 days (for daily clinical administration)
- **Recovery period**
 - Usually ~2 weeks for 28 day study
- **Clinical Observations, Body Weight, Food Consumption**
- **Clinical pathology (clinical chemistry, hematology, coagulation)**
- **Urinalysis, Ophthalmology**
- **Toxicokinetics (TK)**
 - Determine drug profile and accumulation Day1 vs. Day 28
- **Histopathology (all tissues)**
- **Identify MTD and No Observable Adverse Effect Level (NOAEL)**



Standard Toxicology Study Design

Test Article -Treated Rat

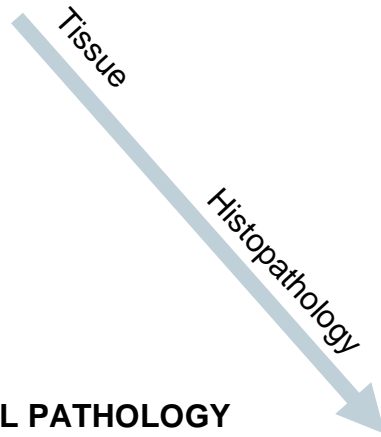
- Collect target organs and other tissues
- Blood samples



Plasma



Tissue

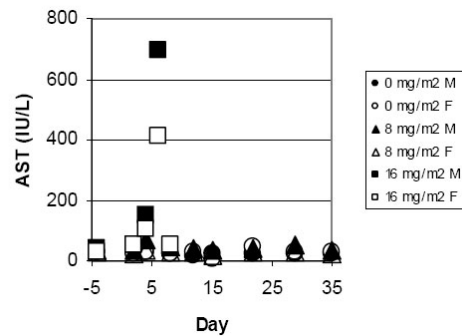


Histopathology

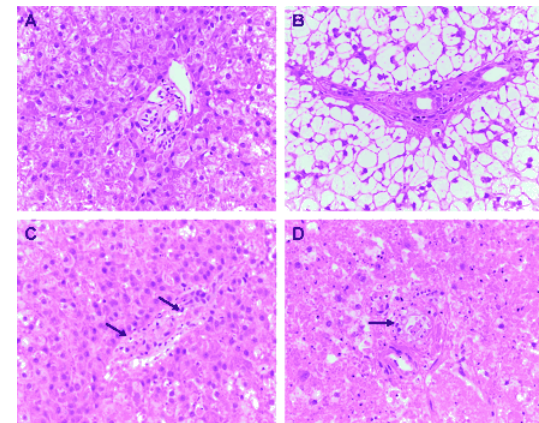
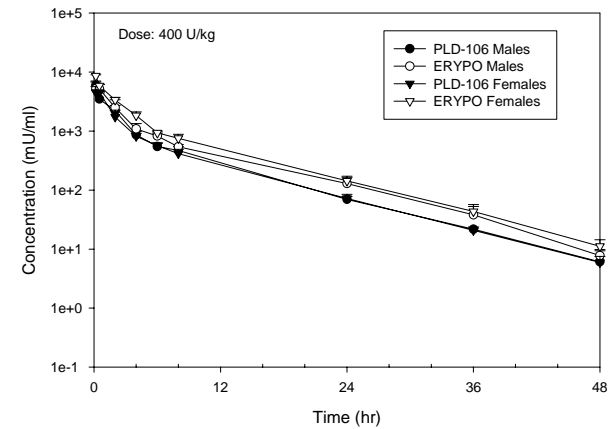
Blood



CLINICAL PATHOLOGY



DRUG ANALYSIS



Effects of hepatotoxic drugs on liver

CLINICAL ENDPOINTS

- Clinical signs
- Body weight
- Food consumption

Safety Pharmacology Core Battery (GLP)

generally required for all regulatory submissions

*• Central Nervous System

- Tier I = Functional Observational Battery (FOB, aka Irwin test)
- Evaluate motor activity, behavioral changes, coordination
- Rats (up to 10/gender/dose group)
- Single dose by intended route
- Control (vehicle) + Test Article (low, mid, high)
- Follow-up with appropriate Tier II tests

• Cardiovascular System

- Electrocardiograms (QTc interval), heart rate, blood pressure
- Beagle dogs (both genders, may re-use dogs after washout period)
- Single dose by intended route
- Measurements/reading up to 24 hours post dose
- Baseline + Dose escalation (low, mid, high)

• Respiratory System

- Measure tidal volume and respiratory rate
- Rats (up to 10/gender/dose)



Ref: ICH S7 guidelines



Genetic Toxicology (GLP)

generally required for all regulatory submissions

- **Bacterial Reversion Assay**
 - *Salmonella/E.coli* Reverse Mutation Assay (Ames Test)
- **Micronucleus assay**
 - May be performed as part of GLP tox study
- **Other genetox**
 - mouse lymphoma assay
 - CHO chrom abs



Other studies

...not an exhaustive list

- Immunology
- Ocular
- Dermal
- Lifetime (\approx 2 yrs) studies
- Reproductive toxicology
- Devices <http://www.fda.gov/cdrh/index.html>



GMP API Preparation

...what you made in the lab cannot be used in the clinic*

*with some exceptions

- **Define clinical API form**
 - free acid/base, salt, counter ion, polymorph
 - physical and formulation stability
- **Process Development**
 - Re-tooling the synthetic process for scale up (mg → kg)
- **Impurities/Contaminants**
 - Identify and qualify
- **GMP production**
 - GMP regulatory compliant facility
 - This is where API and formulation are prepared
 - Goal: prevent drug contamination with non drug materials



GMP = U.S. FDA Good Manufacturing Practices



Discovery → Development Chemistries

...from milligrams → kilograms

• Discovery (Medicinal)

- Maximize number of analogs
- Salts and polymorphs not defined
 - Focus on biological activity
- Low purity $\geq 90\%$
 - Impurities usually not defined
- Cost unimportant
 - Working with milligram quantities

• Development (Preclinical)

- Maximize yield/purity of 1-2 analogs
- Salt form or polymorph defined
 - Focus on scalability & formulation
- High purity $\geq 98\%+$
 - Impurities defined and qualified
 - $\geq 0.05\%$ must be reported
 - $\geq 0.1\%$ must be qualified with Tox studies
- Cost of manufacturing
 - Availability, safety, purity, yield



Above describes the process for small molecules. Similar scale up issues/concerns also exist for large molecules, biologicals, etc.



Chemistry, Manufacturing and Controls (CMC)

- Analytical Chemistry
 - Method development, validation, transfer
 - Bulk and formulation stability testing
- Full Formulation development
 - Enhance solubility, stability
 - Improve bioavailability
 - Novel formulations to extend patent life
- Clinical Trial Materials
 - cGMP manufacturing
 - Custom packaging, repository, distribution
 - CMC documentation



GLPs and GMPs

...paperwork, paperwork, paperwork

- **U.S. Code of Federal Regulations (CFR)**

<http://www.washingtonwatchdog.org/documents/cfr/index.html>

- **CFR Title 21 Food and Drugs**

<http://www.washingtonwatchdog.org/documents/cfr/title21/index.html>

- **Part 58 FDA Good Laboratory Practices (GLP)**

- **Parts 210 & 211 FDA Good Manufacturing Practices (GMP)**

- Subchapter H – Devices

- <http://www.fda.gov/cder/guidance/index.htm>

- **ICH guidelines (European Regulations)**

<http://www.ich.org/cache/compo/276-254-1.html>

- The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)

- **Japanese Regulations**

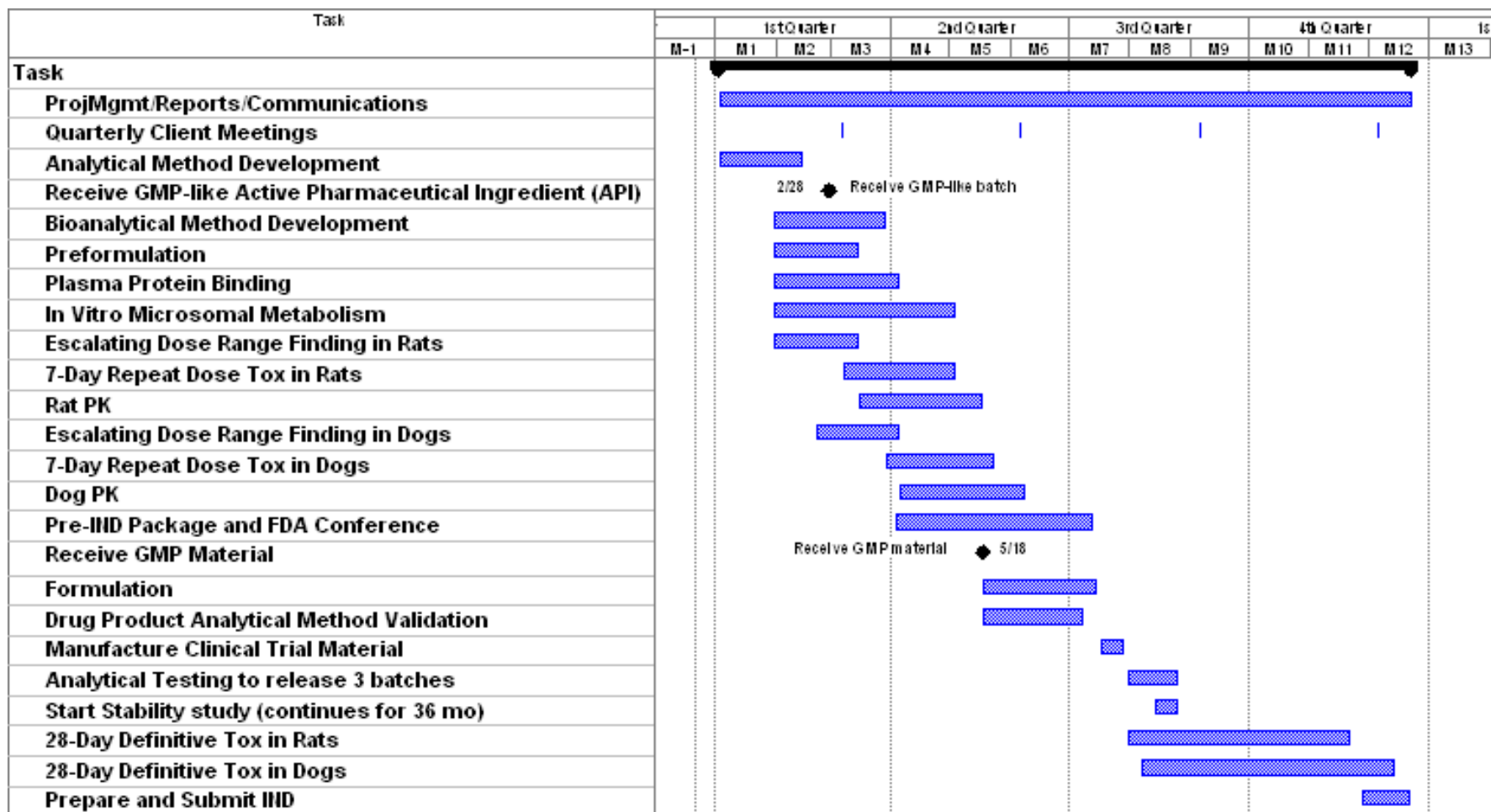


Regulatory Support

- Quality Assurance
 - GLP, GMP, ISO 17025 compliance
 - In-life inspections, data and report audits
 - Maintain Master Schedule
 - Review SOPs and in-house documentation
 - Interact with regulatory inspectors (e.g. FDA)
- Regulatory Affairs
 - Design of preclinical programs
 - FDA pre-IND meetings
 - IND preparation and filing
 - Electronic submissions



Development Plan Timeline



...and finally, there are always exception to the rules.

“You can use an alternative approach if such an approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach contact the FDA staff responsible for implementing this guidance...”

U.S. FDA Redbook 2000



Office of Food Additive Safety, *Redbook 2000: Toxicological Principles for the Safety Assessment of Food Ingredients*, July 2000; Updated October 2001, November 2003, April 2004, February 2006



Helpful Links

- **U.S. FDA Guidance Documents**

<http://www.fda.gov/opacom/morechoices/industry/guidedc.htm>

- **U.S. FDA Fast Track**

<http://www.fda.gov/cber/gdlns/fsttrk.htm>

- **FDA “Redbook 2000”**

<http://www.cfsan.fda.gov/~redbook/red-toca.html>

- **ICH Guidelines**

<http://www.ich.org/cache/compo/276-254-1.html>

Goto: Publications → Guidelines

- **ISO website**

<http://www.iso.org/iso/en/ISOOnline.frontpage>

- **Allometric Dose Scaling Calculator**

<http://www.fda.gov/cder/cancer/animalframe.htm>



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