This Discussion

- Research and Development
- Product development
- Preclinical studies
- Toxicology studies (PK, ADME)
- GLP toxicology studies
- IND package

*Lessons learned
  - Success stories and what it took
  - Failure stories and what went wrong
What are all these letters??

- IND: Investigational New Drug application
- NDA: New Drug Application
- BLA: Biologic License Application
- GLP: Good Laboratory Practice
- GMP: Good Manufacturing Practice
- GCP: Good Clinical Practice
- CMC: Chemistry, Manufacturing and Control
- RMP: Risk Management Plan
- CDER/CBER: FDA’s Center for Drug Evaluation and Research; Center for Biologics Evaluation and Research
The Funnel: Translating a Discovery into a Product

Commercialized Product
Keep the End in Mind!
The Funnel: Keep the End in Mind

Commercialized Product
Package Insert

- What does it do?
- Who will it treat?
- How long will it be used?
- How will it be given?

Regulations and Standards apply to each step

R & D
Preclinical
Clinical
Label/Package Insert/Prescribing Information

- Read a few this week! Story of the drug
- Drafting label early forces team to define specific claims, consider final dosage form and packaging
- Details will change as project progresses; review and update draft PI after each clinical study
- Input from marketing…focus on claims with most value
Preclinical Flow Diagram

Key: manufacturing (red), analytical (grey), documentation (orange), safety (blue), clinical (green)
Ref: Steinmetz et al, 2009
R & D

*Lesson learned – completed R&D and beyond, presenting all of it at conferences – no IP

*Lesson learned – developing candidate B, but 3 big pharmas were in Phase III already

*Lesson learned – wanted to sell it’s drug early in dev, but investors wanted to bring it to market

*Lesson learned – plowed through full dev path without realizing Orphan Drug Indication/fast track

How predictive is the disease model to the disease in humans?
Preclinical: Product Development

- Establish assays necessary for product release
  - Based on MOA
  - Robust and reproducible
- Perform stability studies early
  - Storage
  - Administration
- Consider animal and clinical paradigm early
  - Formulation
  - Route of administration
  - Monitor biodistribution
Preclinical: “CMC” (Chemistry, Manufacturing, and Controls)

1. Identity – active and other ingredients
2. Purity – contamination, chemicals, etc.
3. Potency – based on mechanism of action
4. Safety – biodistribution, toxicology
Preclinical: Product Development

Based on initial PK/PD; THINK ABOUT MANUFACTURING COSTS

Active Pharmaceutical Ingredient; Select suppliers with Drug Master File (DMF) & Tech package

Methods for product characterization; GMP in-process do not need validation until PhII/III; qualification prior to PhI

For tox studies; be sure previous steps are complete (tox $/time)

Start broad with ‘Tentative DPS’

Accelerated & real time; device/packaging included; expiration dating; THINK STORAGE/ ADMINISTRATION/ DURATION OF TX

*Lesson learned - dissolution issue seen only after testing for 3m
Preclinical: Animal Studies

**Animal POC/prelim safety**
Proof your candidate ‘works’ in an APPROPRIATE model

*Lesson Learned: no oversight of CRO

**Animal PK/PD/ADME**
AUC, Cmax, Tmax, T1/2; Selection of dose and regime; bioanalytical assay to measure drug in blood/tissue

CRO – validation

*Lesson Learned – metabolism in dogs; cross BBB

**Reprotox/Mutagenicity/Carcinogenic.**
Proof your candidate is safe

CRO: GLP

*Lesson Learned – did not need these (pre:IND mtg)

**Compatibility**
Devices, combo products, drug delivery (local tolerance, etc)

CRO: GLP

**Animal Tox**
Full safety; therapeutic index for clinical starting dose; single & repeat: dose; acute & chronic; 2 species (be sure of same physiology!)

CRO: GLP
Manufacturers: Key parameters

- Stability (accelerated & real time; shelf life, expiration date)
- Product Control (specifications and certification/testing of raw materials)
- Finished Product Evaluation (testing components and release of batches prior to shipment, stability testing, formula change control)
- Stability/Analytical/Physical/Micro method development
- QA/QC finished product release specifications; C of As
- In-Process Control (batch record to document addition of each ingredient, minimum ingredient)
- ID secondary manufacturer
- Forecast bulk ingredients to ensure supply
- SOPs both at Manufacturing sites, and at sponsor headquarters
Flow of Manufacturing

- **API**
  - Manufacturing
  - Analytical testing
  - Finished Goods-Packaging
  - 3rd Party Logistics
    - Wholesale
    - Retail Pharmacy
    - LTC
    - Specialty Pharmacy
  - Patient

- **QC**
  - Printing of boxes, PI, guides
    - Agreements, Liability insurance

NDC # is required
Clinical Development Strategy

- Clinical Trial Synopsis and Protocol
- Key Opinion Leaders (KOL) and Scientific advisory panels
  - Medical and scientific support for regulatory submission components
- Publications
  - Scientific communications and manuscripts / abstracts / posters
**IND Table of Contents**

1. Form FDA 1571  
   [21 CFR 312.23(a)(1)]
2. Table of contents  
   [21 CFR 312.23(a)(2)]
3. Introductory statement  
   [21 CFR 312.23(a)(3)]
4. General investigational plan  
   [21 CFR 312.23(a)(3)]
5. Investigator's brochure  
   [21 CFR 312.23(a)(5)]
6. Protocol(s)  
   [21 CFR 312.23(a)(6)]
   a. Study protocols  
   [21 CFR 312.23(a)(6)]
   b. Investigator data  
   [21 CFR 312.23(a)(6)(iii)(b)]
   c. Institutional review board data  
   [21 CFR 312.23(a)(6)(iii)(b)]
7. Chemistry, manufacturing, and control data  
   [21 CFR 312.23(a)(7)]
8. Pharmacology and toxicology data  
   [21 CFR 312.23(a)(8)]
9. Previous human experience  
   [21 CFR 312.23(a)(8)]
10. Additional information  
    [21 CFR 312.23(a)(10)]
‘Locked and Loaded’
Make-or-Break Moment
Interacting with the Agency

Answer questions rather than assume
Months of project time and money can be wasted due to guessing what the FDA will say.

Pre-IND Meeting
Not required but nip issues in the bud
Ensure preclinical package supports planned clinical trials

Prepare well
‘The Bibles’
Freedom of Information (FOI)
Summary Basis of Approval (SBA)
Advisory Panel meetings

Go in with YOUR plan, not open arms!
Critical to get FDA buy-in prior to trial start re: sample size, endpoints, stats (what is success?)
Preclinical Flow Diagram

Key: manufacturing (red), analytical (grey), documentation (orange), safety (blue), clinical (green)
Ref: Steinmetz et al, 2009
Cash Flow Valley of Death

[Diagram showing the cash flow valley of death with stages of discovery, preclinical development, early clinical trials, early commercialization, and examples of funding sources in both public and private sectors.]

Balancing Act

**Valley of Death**
Tight budgets often call for ‘short cuts’ in development

**Pay now or Pay later**
Taking too many shortcuts may require additional studies ($) later, or may inhibit partnering with those that have $.

*Lesson learned – too many to count!*
Conclusions

- Review FDA Regulations early in development
  - The translation of discoveries to products will occur more efficiently (and with less stress!)
- Start with the final product label in mind
- Pay now or pay later…
- Keep an eye on the competition
- Many scientific disciplines are required for successful development of candidate into a new medicine
  - That is what makes it so challenging and interesting!
BACKUP / DETAILED SLIDES
# Preclinical and Nonclinical Studies

<table>
<thead>
<tr>
<th>nonGLP and GLP animal testing</th>
<th>IND</th>
<th>GLP animal testing</th>
<th>NDA</th>
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<tbody>
<tr>
<td><strong>Pharmacology</strong></td>
<td>Gene Tox</td>
<td>Metabolism</td>
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<td>Efficacy studies</td>
<td>Ames test</td>
<td>Distribution (radiolabel)</td>
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<td></td>
<td>chromosome aberration</td>
<td>Subchronic tox</td>
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<tr>
<td><strong>Pharmacokinetics</strong></td>
<td><em>in vivo</em> micronucleus</td>
<td>Chronic tox</td>
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<tr>
<td>ADME</td>
<td></td>
<td>(rats-6 month, dog/primate 9-12 months)</td>
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<tr>
<td>absorption</td>
<td>Local tolerance</td>
<td>Toxicokinetics</td>
<td></td>
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<tr>
<td>distribution</td>
<td>- eye/skin irritation</td>
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<td></td>
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<tr>
<td>metabolism</td>
<td>Toxicology in 2 species:</td>
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<tr>
<td>excretion</td>
<td>single-dose tox</td>
<td>Seg II – rat/rabbit teratogenicity</td>
<td></td>
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<tr>
<td>P450 inhibition/induction</td>
<td>repeat-dose tox</td>
<td>Seg I – male/female fertility</td>
<td></td>
</tr>
<tr>
<td><em>In vitro</em> metabolism</td>
<td>(2 weeks to 3 months)</td>
<td>Seg III - pre- and post-natal</td>
<td></td>
</tr>
<tr>
<td>Allometric scaling</td>
<td>toxicokinetics</td>
<td>Carcinogenicity (rat/mouse)</td>
<td></td>
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<tr>
<td><strong>Safety Pharmacology</strong></td>
<td>Identify:</td>
<td>Special studies:</td>
<td></td>
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<tr>
<td>cardiovascular</td>
<td>target organ</td>
<td>immunotoxicity</td>
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<tr>
<td>CNS</td>
<td>NOAEL</td>
<td>comparability studies</td>
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<tr>
<td>respiratory</td>
<td>MTD</td>
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<td></td>
<td>Therapeutic Index</td>
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Borrowed from George Shopp
Duration of Toxicology Studies

**Table 1** Recommended Duration of Repeated-Dose Toxicity Studies to Support the Conduct of Clinical Trials

<table>
<thead>
<tr>
<th>Maximum Duration of Clinical Trial</th>
<th>Recommended Minimum Duration of Repeated-Dose Toxicity Studies to Support Clinical Trials</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Rodents</td>
</tr>
<tr>
<td>Up to 2 weeks</td>
<td>2 weeks&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Between 2 weeks and 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>
</tbody>
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<sup>a</sup> In the United States, as an alternative to 2-week studies, extended single-dose toxicity studies (see footnote c in Table 3) can support single-dose human trials. Clinical studies of less than 14 days can be supported with toxicity studies of the same duration as the proposed clinical study.

**Table 2** Recommended Duration of Repeated-Dose Toxicity Studies to Support Marketing

<table>
<thead>
<tr>
<th>Duration of Indicated Treatment</th>
<th>Rodent</th>
<th>Nonrodent</th>
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<tbody>
<tr>
<td>Up to 2 weeks</td>
<td>1 month</td>
<td>1 month</td>
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<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&lt;sup&gt;c&lt;/sup&gt;</td>
<td>9 months&lt;sup&gt;c,d&lt;/sup&gt;</td>
</tr>
</tbody>
</table>
Tox Studies

- **Genotox:**
  - Usually not required if biologically irrelevant
  - Test contaminants
  - Use relevant assay

- **Carcinogenicity –**
  - In rat and mouse
  - 2 year in length
  - Often difficult route of exposure for 2-year study, e.g., IV, ICV
  - Not generally required unless scientifically justified
  - Assays can include p53 or Tg.AC transgenic models, SHE cell assay (Syrian hamster embryo), *in vitro* assays (e.g., 3T3 transformation assay), nude mouse xenograft models, mice transfected with human protein
Tox Studies

- **ReproTox**
  - Segment I – fertility (testis histopath, sperm mobility, menstrual cycling)
  - Segment II – teratology (developmental tox) – organogenesis, placental transfer
  - Segment III – prenatal/postnatal (secretion of drug in milk)

- **Immunotoxicology**
  - Many biologic therapeutics are immunomodulators – that is their MOA
  - Potential effects on: innate immunity (macrophage, neutrophil, NK cells, acquired immunity - cellular (T cell cytotoxicity) and humoral (antibody response), host resistance (bacterial, viral, tumor)
Vaccines

- Preventive vs Therapeutic
- Pharmacology
  - Preclinical immunization regimen studies not always clinically predictive
  - Protection (efficacy) should be shown in animals if relevant infectious or tumor models
  - PK not generally required; ADME may be required (lymph accumulation)
- Toxicology
  - Local tolerance, repeated dose studies, adjuvant toxicity
  - Species must have similar immune response as humans
- Release testing
  - In vivo bioassay may be required