How Much Animal Data are Required to Move into Clinical Testing?

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Guidances

• FDA is Guidance Driven
  – Good news: guidances are on FDA’s website
    • ICH M3 for small molecules
    • ICH S6 for large molecules
  – In general, FDA will follow these guidances closely
    • Regulatory climate is more conservative, so cannot simply look at past examples to understand how FDA will regulate today
    • Exceptions: oncology and life threatening diseases for which there are only limited treatment options
ICH M3 – small molecules

- Nonclinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals
- Gives detailed description of all the animal studies needed to open an IND, and to NDA (marketing) filing
- Does not tell you how to interpret the studies
ICH M3

• To open a standard IND
  – Pharmacology (efficacy; animal proof of principle) studies
  – A rodent general toxicology study of at least 14 days duration
  – A non-rodent general toxicology study of at least 14 days duration
  – Genotoxicity studies
  – Safety pharmacology studies
  – ADME
  – Analytical assays
General toxicology studies

- Generally daily dosing by the same route of administration intended in the clinic
- Rat or Mouse? Dog or Monkey?
  - Relevant species
    - Metabolism similar to humans
    - Pharmacology
      - Species should have the pharmacological target
      - Some species very sensitive to some drugs
        » Eg rats and NSAIDS, dogs and glucocorticoid steroids
    - Practicality in terms of amount of drug available
- Dose levels
  - Usually 3 dose groups and a control
    - Want to see toxicity at highest dose
    - Would like to see no toxicity at low doses that are near the clinical dose
    - Typical safety factor between a “clean” dose level (NOAEL = no observed adverse effects level) and the clinical starting dose is 10X based on mg/m²
- In addition to your 14 day studies, you generally perform a single dose IV study so you can evaluate bioavailability
General toxicology

• Observations:
  – body weights: daily
  – food consumption: daily
  – cageside: 1-2 times per day
  – plasma samples for PK analysis: last day of dosing
  – clinical pathology: end of study, and before study start for large animals
  – Necropsy: end
  – Histopathology: end

• GLP
Genotoxicity tests

• ICH Guidance on technical issues and which tests are required
• Two in vitro tests to open IND
  – Mutagenicity (Ames)
    • Test in several bacterial strains looking for DNA damage
  – Clastogenicity
    • Test to evaluate chromosome damage
• Not expensive or time consuming…
  Unless the result is positive!!!
Safety Pharmacology

• Additional ICH guidance on safety pharmacology testing
• Focus on 3 systems that if affected could result in death
• Single dose studies
• Highest dose should be “somewhat toxic” (maximum tolerated dose)
  – Reason: experience has shown that findings at high doses are sometimes predictive of effects in humans following repeat doses, e.g. terfenadine
Safety Pharmacology

- Respiratory
  - Single dose rat study; some labs can incorporate this into the CVS study

- CVS
  - Single dose telemetry in dogs or monkeys
    - Animals can be returned to the colony; can also use non-naïve animals
  - hERG (in vitro test for potassium channel activity)

- CNS
  - Single dose rat study
  - Behavioral evaluation
  - Personal opinion: of little value
ADME

- Absorption, distribution, metabolism, and excretion
- Information is collected over the entire course of development
  - At the IND filing stage, you should be starting to get an understanding on the ADME basics of your drug
- Analytic assay(s) is often the hardest part of getting started
ADME

• Generally get exposure data (AUC, Cmax) from general toxicology studies
  – Rodents: add extra animals (many)
  – Dogs or monkeys: use tox animals

• In vitro metabolism generally done
  – Liver microsomes or hepatocytes
  – Compare test species and humans
  – Beginning to prepare for in vivo evaluations

• Distribution and excretion data may be collected; varies with different drugs and people
Analytical assays

• Need to quantify dose formulations for your GLP studies
• Needed to quantify plasma levels
• If complex metabolism, need over time to have an analytical assay for all major metabolites
• Need to quantify impurities and be sure you are below ICH levels
• A lot of work!
ICH S6 -- biologics

- Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals
- General toxicology
  - Usually monkey
  - Changing requirements on rodent
- No genotoxicity testing
- Safety pharmacology needed
- Immunogenicity (monoclonal antibodies)
- Some ADME
Biologics challenge

- Regulatory oversight of biologics has changed from CBER to CDER (center for biologics to center for drugs)
- Small molecule M3 people are now regulating S6
  - S6 is fairly general
  - Allowed CBER to not request many studies
    BUT now it allows CDER to request many studies
Other items

• What was described above summarize the regulatory requirements. Other things are needed to support your program outside of regulatory requirements
  – Short, nonGLP studies to identify dose levels for your GLP studies
  – Screening assays often done to select the best candidates for GLP studies
    • Receptor binding, Ames, hERG are common screens
  – Getting sufficient drug to perform toxicology studies often takes 9-12 months, and is the classic underestimated step
Example

• NME: Supernova drug
  – Anti-inflammatory activity = “immunomodulator”
  – First chosen indication: oral drug for psoriasis
  – Pharmacology studies completed, support indication
  – Would like to file IND
  – Work out timelines
  • 6 months needed to scale up mfg to make drug
Example

• Have small amount of drug already made for bench work
• Use drug to perform screening tests
  – Ames is negative
  – hERG is positive
• Decision: drop lead candidate because of positive hERG, or scale up and perform complete CVS evaluation?
  – Most would drop the drug
Example

• Decide to scale up
• Go into non GLP dose finding studies
  – Rats die at dose levels that, based on pharmacology, are needed for the clinical dose for efficacy
  – Dogs are fine
• Decision: drop this drug, knowing that rat findings are generally about 50% effective?
Example

- You love this drug. You decide to move forward.
- Perform a full hERG assay – it is a clear positive
- Dog telemetry study is clean – no in vivo effects
- Decision: stop development because of the positive hERG?
Example

• You cannot believe your bad luck. The lab must have made a mistake. You know this is a great drug.
  – You decide to go forward.

• You spend $500K to perform your GLP rat and dog studies
  – The dog tolerates doses up to 1000 mg/kg
    • See liver effects at highest dose
  – Rat does not tolerate drug
    • NOAEL is 1 mg/kg
      – You will need a 10X safety factor
Example

- You are lucky!
- The rat toxicity is monitorable.
- Clinical pathology can be monitored in humans before histopathological doses
- FDA makes you start at a very low dose, but you are allowed to dose upward with careful monitoring
- Your human study demonstrates that the rat is more sensitive to the drug than humans
NME vs. Old drugs

• What is described above is for new molecular entities
• For already approved drugs, fewer animal studies may be needed
• Varies with what was done for the “innovator molecule”
  – IF there are no patent issues, you have the right to “use” the innovator’s data to support your application
  – 505(b)2
Example

• Budesonide
  – Glucocorticosteroid
  – Off patent
  – No inhaled generic steroids allowed by FDA
    • Because cannot be quantified in PK study
  – A full set of toxicology studies, including carcinogenicity and repro. studies done
  – Entire tox package for “new” products using old ingredient is two 2-week studies and one 90 day study for the NDA
Example 2

- Ibuproferin
  - No patent issues
  - Want to develop it for localized chronic pain
  - Because no topical studies have been done, a complete dermal toxicology package, including carcinogenicity testing, would be required

- Message: the devil is in the details
Beyond the IND

• Your general toxicology studies must at least be equal in length (with finalized study reports) to the length of your clinical trials
  – E.g. 14 days only supports up to 14 days in the clinic

• As you progress, many additional nonclinical studies are required

• Development is constant
Summary

• FDA is increasingly conservative, and less likely to “give you a break”
• Guidances describe needed studies
  – They require a lot of time and money
• Results count! Even if you have planned and implemented the perfect program, if a drug is toxic at clinically relevant doses, the IND may never go forward
• PreIND meetings with the FDA are a useful place to communicate with your regulator