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 does 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/m^2
- 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 phamacology 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