

# Regulatory Path for Nonclinical Studies to Support Development of Broad Spectrum Therapeutics

## Pharmacology/Toxicology

William H. Taylor, Ph.D., DABT  
Pharmacology/Toxicology Team Leader  
FDA/CDER/Office of New Drugs/  
Office of Antimicrobial Products/  
Division of Special Pathogen and Transplant  
Products

# Drug Regulations

- ▶ Federal Food, Drug and Cosmetic Act
- ▶ Title 21 Code of Federal Regulations

21 CFR 58 Good Laboratory Practices

21 CFR 201.57 Labeling

21 CFR 312.23 IND content & format

21 CFR 314.50 NDA content & format

# Pharmacology/Toxicology Guidance

## Final Documents

- ▶ 15 CDER Pharm/Tox Guidances
- ▶ 14 ICH Safety Pharmacology Guidances

## Draft Documents

- ▶ 4 CDER Pharm/Tox Guidances
- ▶ 1 ICH Safety Pharmacology Guidances

ICH = International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use.

# Nonclinical Studies (1)

## Prior to Phase 1 Clinical Trials

- ▶ Single dose (acute) or dose escalation or dose range-finding studies
- ▶ Safety pharmacology studies: examine cardiovascular, CNS, respiratory endpoints
- ▶ Local tolerance studies

# Nonclinical Studies (2)

## Prior to Phase 1 Clinical Trials (Cont.)

- ▶ Toxicokinetic/Pharmacokinetic (i.e., plasma) studies
- ▶ In vitro genotoxicity studies (two)
- ▶ Complete reproductive battery and genotoxicity battery *if* enrolling pregnant women in clinical studies

# Nonclinical Studies (3)

## Prior to Phase 2 Clinical Trials

- ▶ Toxicokinetic/Pharmacokinetic (i.e., ADME/tissue distribution studies)
- ▶ In vivo genotoxicity study

## Prior to Phase 3 Clinical Trials

- ▶ Female and male fertility
- ▶ Embryo-fetal developmental studies

# Nonclinical Studies (4)

## At Any Time

- ▶ Carcinogenic studies or special toxicity investigations

## With NDA Submission

- ▶ Generally, all nonclinical studies submitted to the IND are submitted to the NDA

## Post-NDA Approval

- ▶ Carcinogenic studies and special toxicity investigations *may* be post-marketing commitments

# Single-Dose Toxicity Studies

- ▶ Used to identify a maximum tolerated dose (MTD) and to select doses for repeat-dose toxicity studies
- ▶ Provides preliminary identification of target tissues
- ▶ May provide information relevant to acute overdosing in humans

# Dose Escalation Studies & Safety Pharm

- ▶ Dose-Range Finding or Dose Escalation Studies are often needed to select range for nonclinical repeat-dose studies
- ▶ Safety pharmacology studies (for cardiovascular, CNS, respiratory) are usually single dose studies and may be conducted alone or as part of other (repeat-dose) studies

# Repeat-Dose Studies (1)

- ▶ Usually are pivotal studies
- ▶ Usually include a TK/PK substudy
- ▶ High dose should elicit significant, but not life-threatening toxicity
- ▶ Recommended tissue list for histopathologic examination available from *Toxicologic Pathology* (2003) Vol 31 No 2 pp. 252-253 and Vol 31 No 5 p. 571

## Repeat-Dose Toxicity Studies (2)

Duration of Clinical Trials	Minimum Duration of Repeat-Dose Toxicity Studies*	
	Rodents	Non-rodents
Single Dose	2 – 4 weeks**	2 weeks
Up to 2 weeks	2 – 4 weeks**	2 weeks
Up to 1 month	1 month	1 month
Up to 3 months	3 months	3 months
Up to 6 months	6 months	6 months***
> 6 months	6 months	Chronic***

# Repeat-Dose Toxicity Studies (3)

## Notes:

- \* Previous Table from ICH-M3 Guidance document
  
- \*\* In the U.S., as an alternative to 2-week studies in rodents, single dose toxicity studies with extended examinations can support single-dose human trials.
  
- \*\*\* Data from 6 months administration in non-rodents should be available before the initiation of clinical trials longer than 3 months. Alternatively, data from a 9-month non-rodent study should be available before the clinical treatment duration is exceeded which is supported by the available toxicity studies.

# Genotoxicity Studies (1)

Standard genotoxicity battery includes:

1. In vitro gene mutation assays in bacteria (Ames test)
2. In vitro evaluation of mammalian cell chromosomal damage, OR  
in vitro mouse lymphoma thymidine kinase (tk) assay
3. In vivo evaluation of chromosomal damage in rodent hematopoietic cells.

HOWEVER...

## Genotoxicity Studies (2)

Antibiotics that kill Gram-negative organisms will kill the bacteria in the Ames assay; therefore:

- ▶ Ames assays using antibiotics that are effective against Gram-negative organisms may not be useful.
- ▶ Consider submitting an alternative in vitro assay, and/or the prescribed in vivo assay prior to Phase 1 clinical trials.

# Reproductive Studies (1)

Standard reproductive battery includes:

F<sub>0</sub> generation

- ▶ Fertility
- ▶ Parturition
- ▶ Lactation

F<sub>1</sub> generation

- ▶ Mortality
- ▶ Structural alterations
- ▶ Growth
- ▶ Function: developmental neurobehavioral & reproductive

## Reproductive Studies (2)

- ▶ Complete reproductive battery is generally expected prior to Phase 1 trials if enrolling pregnant women in clinical studies
- ▶ Otherwise, women of childbearing potential may be included (in the U.S.) in Phase 1 and Phase 2 clinical trials if using effective birth control, have negative pregnancy test, and sign informed consent
- ▶ In the U.S., female fertility and embryo-fetal developmental (nonclinical) studies should be completed prior to enrolling women of childbearing potential in Phase 3 trials

# Reproductive Studies (3)

- ▶ Male reproductive organs are evaluated in nonclinical repeat-dose toxicity studies; further nonclinical studies if warranted
- ▶ Rabbits are generally a poor animal model for antibiotics because antibiotics disrupt their intestinal flora and their digestive abilities and kill them

# Carcinogenicity Studies

- ▶ Sponsor should submit protocols for Agency comment before initiating studies
- ▶ Usually not needed prior to clinical studies
- ▶ Usually not needed for products administered less than 6 months
- ▶ If desiring to omit carcinogenesis studies, request a waiver (and include your rationale)

# Additional Safety Studies (1)

May be needed:

- ▶ if signals are detected in previous nonclinical studies (e.g., immunosuppression)
- ▶ to examine excipients, impurities, or metabolites
- ▶ for pediatrics indications

May be independent or embedded in larger toxicology studies

# Old Drug/ New IND?

- ▶ Consider the old & new: indications, patient populations, dose levels, regimens, formulas, and routes
- ▶ Consider the extent the previous nonclinical studies support the new indications, ...etc.
- ▶ Consider whether clinical data will substitute for shortcomings in nonclinical support

# Animal Rule – Nonclinical (1)

21 CFR 314 Subpart I (drugs)

21 CFR 601 Subpart H (biological products)

- ▶ For approval of products when human efficacy studies are not ethical or feasible
- ▶ Efficacy is primarily established in animals
- ▶ Does not address safety...

## Animal Rule – Nonclinical (2)

However:

- ▶ “FDA will rely on the evidence from studies in animals...only when:
- ▶ (1) There is reasonably well-understood pathophysiological mechanism of the toxicity of the substance and its prevention or substantial reduction by the product; ...”

## Animal Rule – Nonclinical (3)

Therefore,

- ▶ Pivotal safety studies should be conducted in the same animal model as used to show efficacy
- &
- ▶ Rabbits are generally a poor animal model for antibiotics because antibiotics disrupt their intestinal flora and their digestive abilities and kill them