# Considerations for a Genotoxic API in Clinical Trials: Healthy Subjects or Patients?

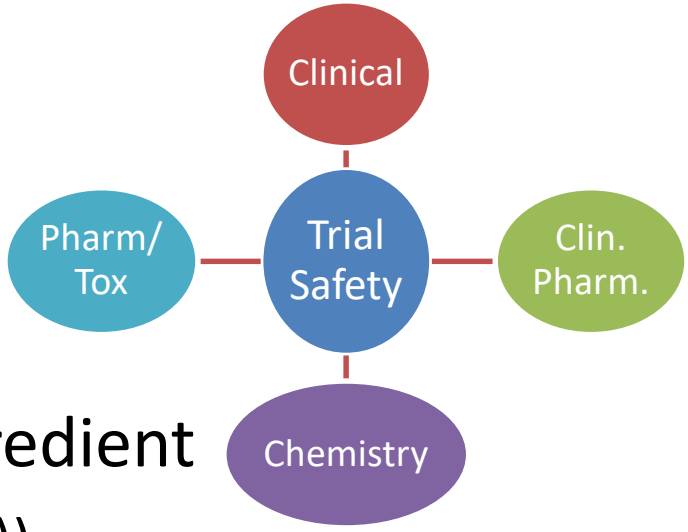
**Robert T. Dorsam, PhD**
**Associate Director of Pharmacology/Toxicology**
**Division of Clinical Review**
**Office of Generic Drugs, CDER/FDA**

# Disclaimer

*This presentation reflects the views of the author and should not be construed to represent FDA's views or policies.*

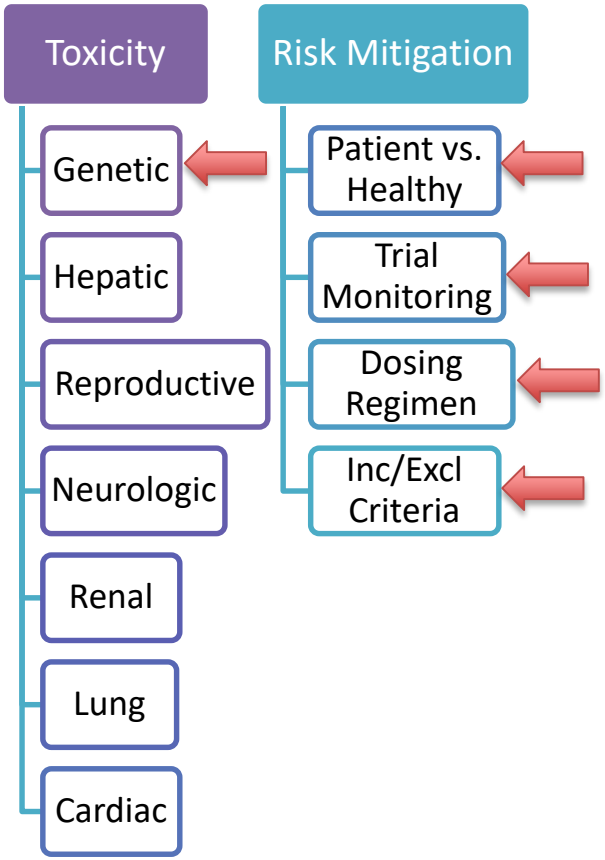
# Background

- Clinical trials are integral to support NDA, BLA, and ANDA submissions
- The safety of clinical trial subjects is a critical multi-disciplinary issue
- The Pharm/Tox discipline assesses the genotoxic risk of the active ingredient
  - In vitro and in vivo studies (ICH S2(R1))
- Genotoxic risk is assessed during clinical trial development, but several areas warrant further consideration



# Clinical Trial Safety

## Clinical trial safety is a complex review issue




- Today, we will focus on genetic toxicity risk
- Genetox study protocols are standardized; ICH S2R1 and ICH M3R2 provide guidance on study interpretation and timing for when the studies are submitted for INDs
- How do we interpret study results into safety considerations for clinical trial subjects?
  - Healthy subjects or patients?
  - What are appropriate mitigation strategies to ensure safety?

# ICH S2(R1) Genetox Battery

ICH guidance recommends a battery of studies to inform genotoxic risk relative to the stage of clinical development

**Option 1**

1. In vitro mutagenicity
   - Bacterial reverse mutation assay
2. In vitro chromosomal damage
   - In vitro chromosomal aberration assay
   - In vitro micronucleus assay
   - In vitro mouse lymphoma Tk gene mutation
3. In vivo genotoxicity
   - In vivo chromosomal damage

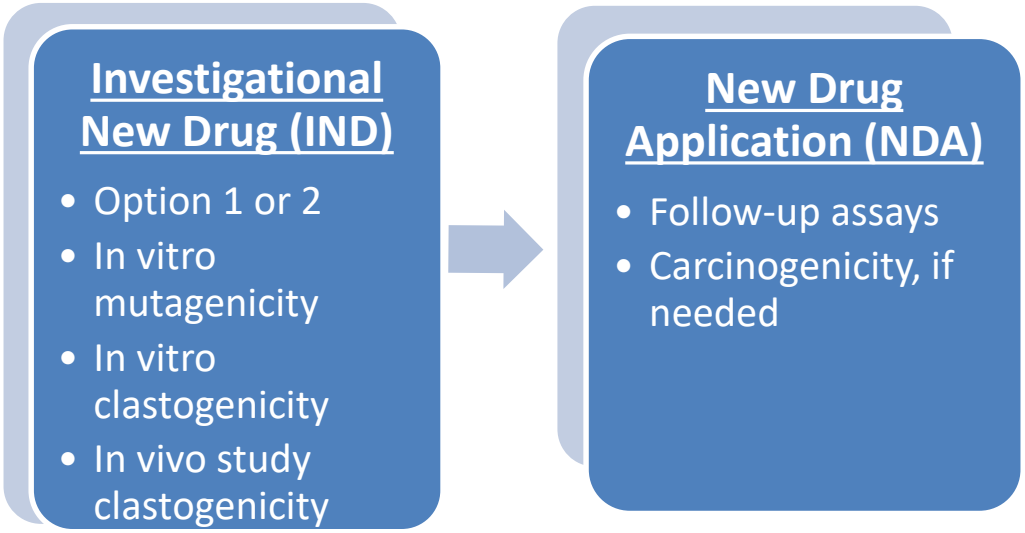
**Mechanisms of Genetic Toxicity**

- Mutagenicity
- Clastogenicity
- Aneuploidy
- Epigenetic modification

**Option 2**

1. In vitro mutagenicity
   - Bacterial reverse mutation assay
2. In vivo genotoxicity assays with two tissues

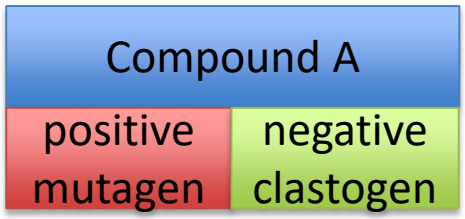
# Assessments relative to clinical development in an IND and NDA

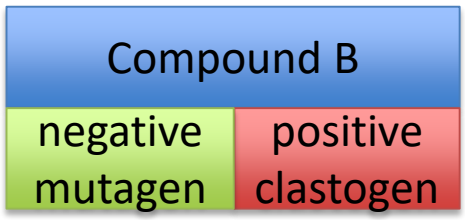



- Pharm/Tox assessors rely on the genetic toxicology battery (ICH S2R1) prior to Phase 1 trials in an IND (ICH M3R2)
  - This is a primary focus for today
- Questions remain about how individual results inform "patient or healthy subjects?" or risk mitigation strategies

# At the IND stage

In vitro mutagenicity, in vitro and/or in vivo clastogenicity information are available before first-in-human trials




## Follow-up assays

- If a drug is genotoxic (mutagenic and/or clastogenic), are there follow-up studies to assess potential risk that should be done prior to conducting studies in healthy subjects?

# Further Questions

## Mechanism

Certain drugs may be clastogenic but not mutagenic. Should consideration be given to the mechanism of action of genotoxicity in designing studies with healthy subjects?

## Considerations on Trial Design

- Does it matter if a healthy volunteer is exposed to a single dose or up to 4 doses of an active ingredient?
  - Is continuous daily dosing acceptable? If so, for how long?
  - If dosing is intermittent, how many doses would be acceptable?

# Dosing in Clinical Trials

The dose level, frequency, and dosing interval may be adjusted for safety

- A single dose, two-way, crossover trial design


Does it matter if a healthy volunteer is exposed to a single dose or up to 4 doses?

Is continuous daily dosing acceptable? If so, for how long?

If dosing is intermittent, how many doses would be acceptable?

Micro-dose (ICH M3R2) – Limit 100 μg/dose

# Later in the Lifecycle: 505(b)(2) and Generics (505(j))

- During development of a 505(b)(2) or 505(j) drug product, genetic toxicology and carcinogenicity information are stated in the reference listed drug (RLD) drug label

**ANDA, 505(b)(2)**

- RLD drug label
- In vitro and in vivo genetox and carcinogenicity assays

- Questions remain about how to weigh results of these studies for clinical trials supporting these applications
  - "Patient or healthy subjects?" and risk mitigation strategies

- A large number of 505(b)(2) applications and ANDAs are submitted to CDER
  - They play a significant role in access to therapies, and safety in their supporting trials is important

**ANDA:** Abbreviated New Drug Application for a proposed generic drug

# Generic Drugs: More Information

- Generic drug applicants need to demonstrate bioequivalence (BE) to the RLD
- BE is demonstrated in trials that will involve either healthy subjects or patients
  - Showing BE by dosing with test and reference product
  - Fasting and fed conditions
  - Safety is a review issue and considers prior use of healthy subjects versus patients during RLD development
- Genetic toxicology data and carcinogenicity information is in the RLD label

# Drug Labels Inform Safety

- We surveyed FDA approved drug labels for APIs that have positive results in genetox or carcinogenicity studies
  - Search Nonclinical Toxicology Section of drug labels for the word “positive” using FDALabel tool
  - Identified 250 non-duplicate APIs. Next, we tabulated positive results of a subset

**FDALabel**

https://nctr-crs.fda.gov/fdalabel/ui/search

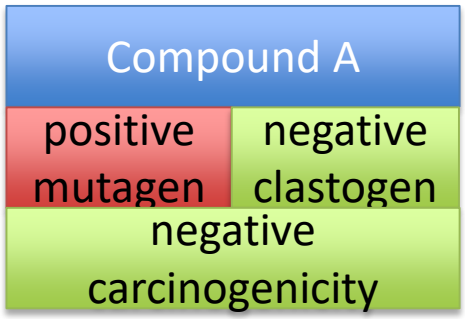
Filter,

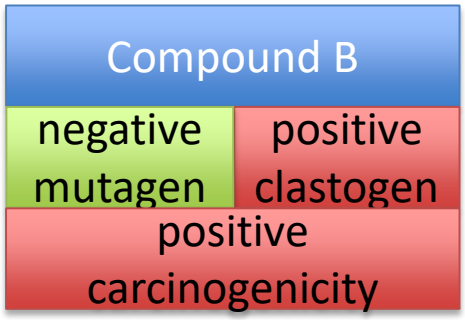
Tabulate

**Genetox Info for APIs**

- Some APIs have a positive result in either in vitro or in vivo assays
  - Examples: APIs that are anti-virals, anti-hypertensives. Therapies for migraine, acid reflux, high cholesterol, arrhythmia, inflammation
- Our aim is to use available information so that trial subjects for BE studies are put at no greater risk than in other trials

# Generic Drugs: More info, now what?




- Should a weight-of-evidence* approach be used to decide whether a compound should be tested in bioequivalence studies with healthy subjects?
  - If yes, which test results should receive greatest consideration in the WOE assessment?
  - Are there any other factors relating to genetic toxicology that should be considered when determining if a study should include healthy subjects in bioequivalence studies?

*Weight-of-evidence: as described in ICH S1B and ICH S2(R1)

# Summary of Questions

**Dosing**

- How many doses of an Ames-positive drug (DNA reactive drug) can be safely administered to Healthy Subjects?
  - 1, 2, 3, or 4 doses
  - Is continuous daily dosing acceptable? If so, for how long?
  - If dosing is intermittent, how many doses would be acceptable?

**Follow-up Assay**

Are there appropriate follow-up studies that should be conducted prior to studies in healthy volunteers if an API is Ames-positive?

# Summary of Questions

**Mechanism**

Certain drugs may be clastogenic, but not mutagenic. Should consideration be given to the mechanism of action of genotoxicity in designing studies with healthy volunteers?

**Weight of Evidence**

Should a weight-of-evidence approach be used to decide whether a compound should be tested in bioequivalence studies with healthy subjects?

- If yes, which test results should receive greatest consideration in the WOE assessment?
- Are there any other factors relating to genetic toxicology that should be considered when determining if a study should include healthy subjects in bioequivalence studies?

# Summary

- The safety of trial subjects is of paramount importance
- Genotoxic risk is an important consideration when determining safety for trial subjects
  - The recommended genetox studies are available prior to FIH studies, and more information maybe available at later stages
- “Healthy subjects or patients?” is a key consideration toward risk management for NDAs, BLAs, and ANDAs
  - Other trial design elements may also mitigate risk
- We appreciate the expert panel’s insight into how to best translate available information into an appropriate safety recommendation for participants in clinical trials

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