Impact of data integrity issues on Pharmacology/Toxicology studies in Abbreviated New Drug Applications

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Disclaimer

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Outline

- Introduction to Pharmacology/Toxicology (Pharm/Tox) review in the Office of Generic Drugs (OGD)
- Common data integrity issues and the types of studies that are impacted
- Impact of data integrity issues on review process
- Approaches to manage impact including key collaborations in identifying/investigating these issues

OGD Pharmacology/Toxicology

Consulted when there is a Pharm/Tox safety question

Consulted by Office of Pharmaceutical Quality (OPQ) and divisions within OGD

Conduct context-specific review

Dose, duration of exposure, patient population, and route of administration

Pharm/Tox review in OGD has similarities to the Office of New Drugs

Collaborate frequently on review issues

Apply International Council for Harmonisation (ICH) and FDA guidance

Goal to ensure the same safety profile for the generic as its reference listed drug (RLD)

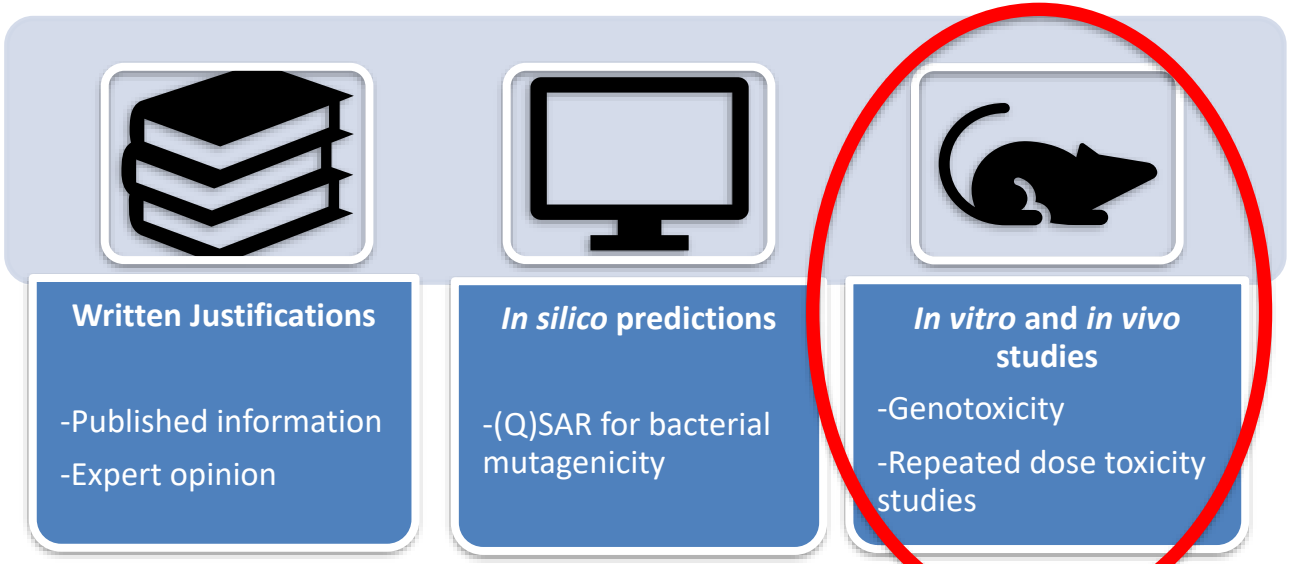
Operates to fulfill OGD's mission: "OGD ensures that high-quality, affordable generic drugs are available to the American public."

What does Pharm/Tox in OGD do?

Review safety of generic formulations

Impurities, excipients, residual solvents, contaminants from container closure

Evaluate toxicology data submitted by Drug Master File (DMF) holders and Abbreviated New Drug Application (ANDA) applicants to support specifications



(Q)SAR = quantitative structure-activity relationship prediction

Studies impacted by data integrity issues

In vitro and in vivo nonclinical studies

Conducted by contract research laboratories on behalf of the sponsor

- Sponsor: DMF holder or ANDA applicant

Genotoxicity and repeated-dose toxicity studies

- Bacterial mutagenicity (Ames)
- Rodent studies

Commonly, a singular nonclinical study is the sole submission to justify safety

- Unique review challenge for ANDAs
- Important that the submitted study is solid and reliable for safety review

Nonclinical studies are not always conducted under Good Laboratory Practice, or "GLP"

GLP compliant studies are preferred

Non-GLP studies are accepted, robust data are necessary

Data integrity issues are not unique to either GLP or non-GLP

What are we looking for?

We review each submitted study individually

Regardless of study type or origin, evaluate each on their own merits

Robust study data and assay validity

Evaluate criteria for positive response, use of appropriate controls, GLP compliance, dosing solution analysis, adherence to standard protocols (OECD, Redbook), etc.

Evaluate study design, dose selection

- Do the doses tested support the proposed clinical exposure?
- Are the models used relevant?

Apply ICH and FDA guidances to make recommendations based on safety data

Data integrity is crucial for OGD Pharm/Tox to assess safety

OECD: Organization for Economic Cooperation and Development

What data integrity issues do we see?

Suspicious data patterns

- Data repetition, biologically implausible data
- Missing information: missing data, incomplete methods or results, unsigned study reports/quality assurance documents
- Claims of “GLP compliance” but not really compliant
- Different species/study, same data!

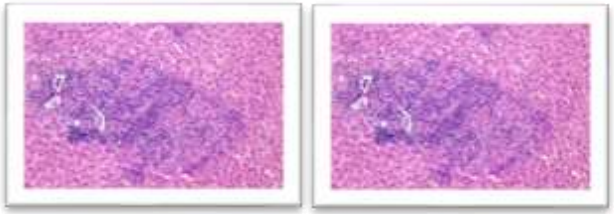
False negative results

- FDA has data to demonstrate positive result, but firm submits negative result
- Raise questions about study integrity (e.g., protocol, conduct, sensitivity)
- Warrants further investigation if “GLP compliant” → GLP inspection
- Warrants further investigation if non-GLP as well

What data integrity issues do we see?

Suspicious data patterns*

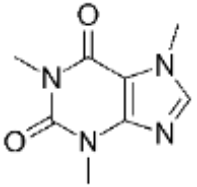
Rat 1 Rat 2



Different animals, same histology picture

100s of rodents, zero clinical signs over the course of a 90-day study

False negative results



Compound A

Mutagenic?

Applicant 1 → Ames Positive

Applicant 2 → Ames Positive

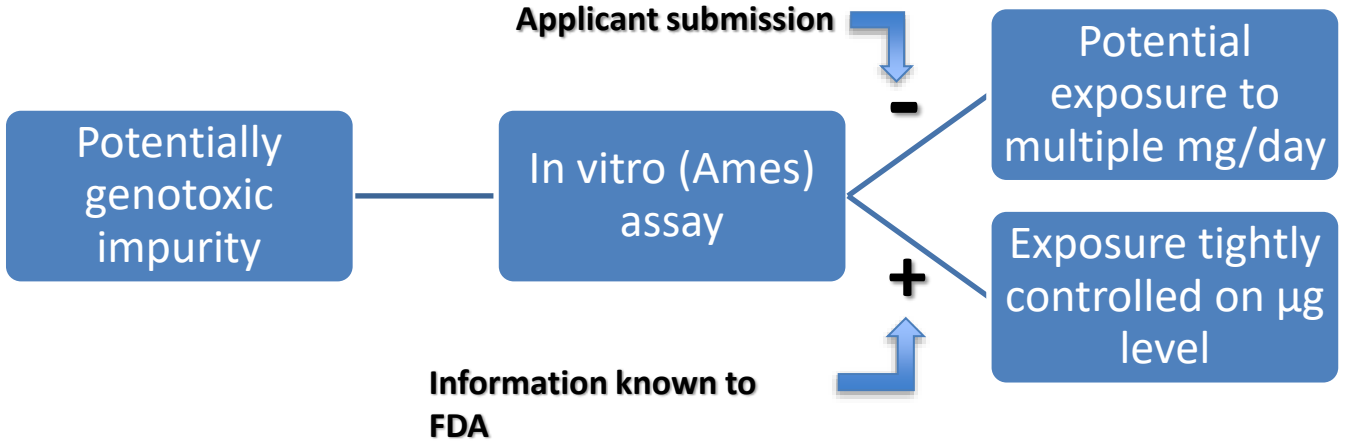
Applicant 3 → Ames Negative

** Images from National Toxicology Program, Nonneoplastic Lesion Atlas*

What is the impact of a nonclinical study?

The results of a nonclinical study inform decision on patient exposure to an impurity

What is the impact of a **data integrity** issue?



False negative assays may result in patient exposure to unsafe levels of an impurity

Data Integrity Issues and Impact

May trigger FDA GLP inspection that is dependent on Pharm/Tox review determination

- FDA GLP inspection timing
  - Data coming from laboratories overseas: coordinating an inspection may take time and impact application goal dates

May trigger investigation with consultation with internal Agency experts

- Internal consultation timelines vary and may delay Pharm/Tox review
- Consultation may involve multiple offices with competing deadlines
- Information Request to the DMF Holder or Applicant to obtain more information from the Contract Research Organization (CRO)

Outcome of inspection, investigation, and review determination affects regulatory action

- If data deemed unreliable, then the outcome may be a Complete Response (CR)

When Data Integrity Issue is with a study from the DMF Holder

DMF information is considered proprietary

ANDA applicant may not know specifics of DMF or DMF deficiencies

ANDA applicant receives a CR if DMF is deficient

Referencing ANDA receives CR for pending drug substance deficiencies

If DMF is referenced by multiple applications → may have broad impact

- Some DMFs are referenced by New Drug Applications (NDAs) and necessitate collaboration with the Office of New Drugs

Impact: potential drug shortages, first generic not ready for approval, etc.

Approaches to Manage Impact

Risk assessment when the submitted study is not reliable

- Search public and internal databases
- Consult with internal review disciplines
  - Computational toxicology experts, RLD review division, Office of Study Integrity and Surveillance
- Attempt to resolve issue with Information Request to obtain information from CRO
- If OGD Pharm/Tox cannot resolve the question of safety in risk assessment: Major deficiency issued in a Complete Response with recommendations for resolution

CRO in question may be supporting multiple applications (ANDAs and NDAs)

- Isolated incident or systemic problem?
- Identified data integrity issues may pose problem for approved applications: How to mitigate risk?
  - Share knowledge within the Agency
  - Review each study individually and identify unusual patterns
  - Keep track of questionable studies for teaching purposes

Recommendations for DMF Holders/Applicants

Data integrity issues arise in both GLP and non-GLP studies

Robustness and validity of study is key

Prior to submitting your study to OGD, evaluate study report for

- Adherence to OECD/Redbook guidelines
- Study robustness
  - Appropriate study design and model
  - Adequate dosing, positive controls
- Adherence to GLP
  - If GLP compliant, check for appropriate documentation and signatures
- Thorough documentation including dosing solution analysis
- Submit full and complete, legible study reports

Summary

OGD Pharm/Tox plays a critical role in safety review of generic drugs

- Evaluation of data integrity is a crucial aspect of review
- Investigate scope of data integrity issues
- May impact multiple applications (isolated versus systemic issues)

OGD Pharm/Tox actively collaborates with internal review disciplines to resolve questions related to data integrity

- Work to mitigate impact of data integrity issue
- Collaborations and knowledge sharing are key

Challenge Question #1

OGD Pharmacology/Toxicology reviews in vitro and in vivo studies for which of the following in generic drug formulations?

A. Impurities
B. Excipients
C. Residual solvents
D. Contaminants from container closure
E. All of the above

Challenge Question #2

True or False: Nonclinical studies must be conducted under GLP because this is an indicator of reliable data.

a) True

b) False

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