Data Integrity in Pharmacology/Toxicology Studies

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Disclaimer

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

Outline

- Introduction to Pharmacology/Toxicology (Pharm/Tox) review in the Office of Generic Drugs (OGD)
- Observed data integrity issues and the types of studies that are impacted
- Case studies of data integrity issues

Role of Pharmacology/Toxicology in Generics

Consulted when there is a Pharm/Tox safety question

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

Conduct context-specific safety 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)

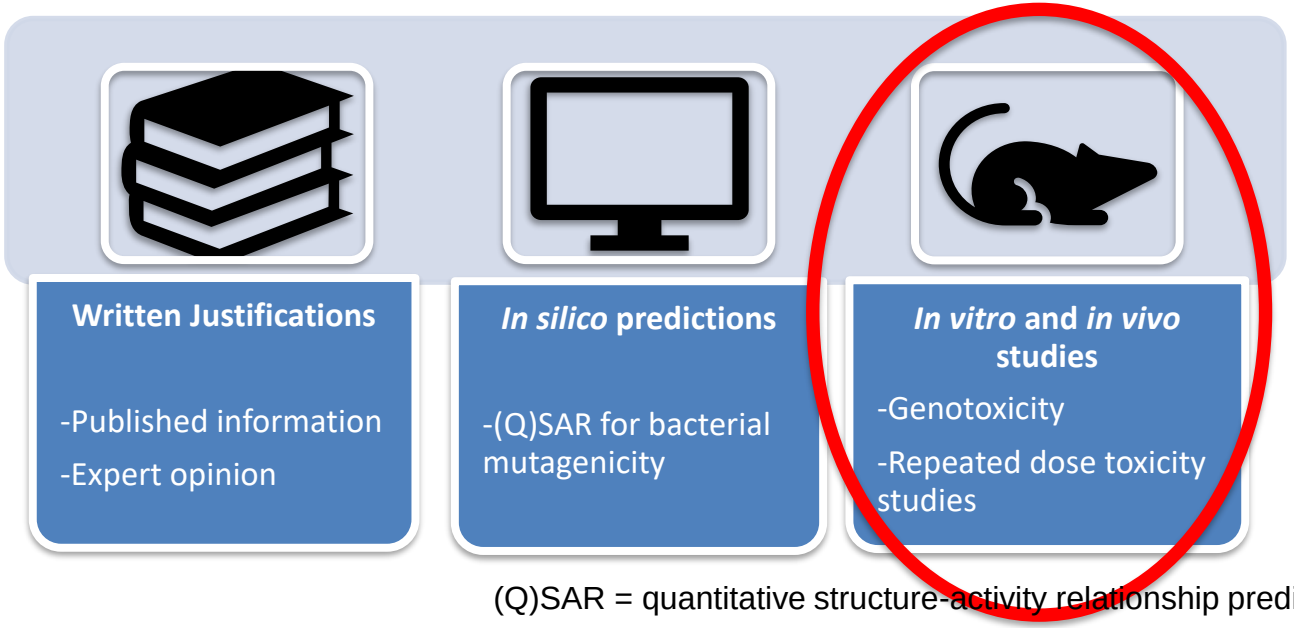
Operates to fulfill OGD's mission: "OGD ensures that high-quality, affordable generic drugs are available to the American public."

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

How does Pharm/Tox assess study data?

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

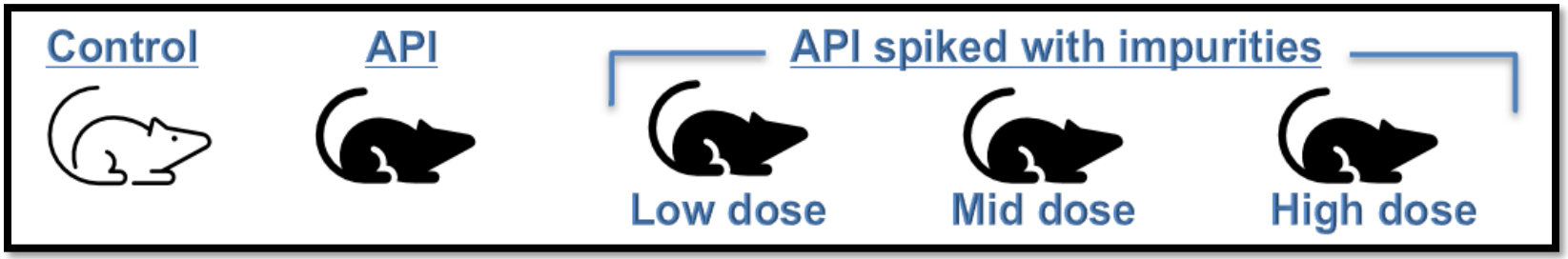
DATA INTEGRITY CASE STUDIES

Case Study 1: Rodent Clinical Observations

90-day oral toxicity study of drug substance spiked with impurities

- Signed FDA GLP compliance statement
- Five dosing groups:

API = active pharmaceutical ingredient



- Number of animals: 10 rats/sex/dosing group = 100
- Methods state clinical observation included 12 parameters including changes in coat, skin, posture, and excretions.
  - Published literature reports that rats experience diarrhea and hunched posture at the dose of API given

Case Study 1: Rodent Clinical Observations

90-day oral toxicity study of drug substance spiked with impurities

– Individual clinical observation of all 100 rats over the course of 90 days

Animal Number	Observation	Day	
		From	To
1	**Normal**	1	90
2	**Normal**	1	90
3	**Normal**	1	90
4	**Normal**	1	90

Case Study 1: Rodent Clinical Observations

Review of other GLP rodent studies submitted to OGD by the same laboratory revealed the same pattern of observations

- All studies submitted contained **100% normal** clinical observations for **all** animals
- Biologically implausible to have zero clinical signs to note across hundreds of animals and across numerous studies
  - 21 CFR 58.31(f): Assure that personnel clearly understand the functions they are to perform
  - 21 CFR 58.130(a): The nonclinical laboratory study shall be conducted in accordance with the protocol

GLP inspection

- Study personnel were not recording the individual clinical signs stated in their protocol
- Cage-side interpretation of clinical signs potentially left out data that should have been recorded and placed in the study report

Results raised questions about study conduct, potential inadequate drug exposure, and ability to interpret the data for a conclusion about safety of the impurity

Case Study 2: False Negative Results

Ames study submitted to justify controlling an impurity as non-mutagenic in a drug product with a chronic indication

Initial review noted that background plates had low survival and weak positive control responses

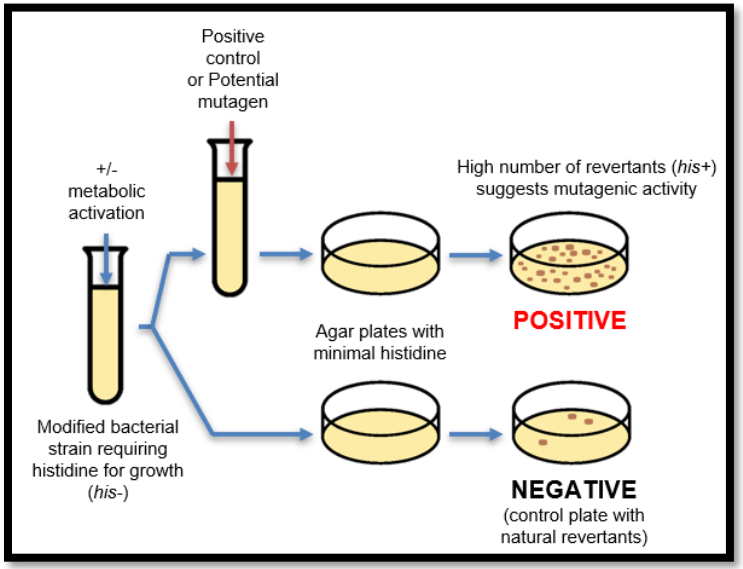
Further search for information on the impurity revealed that this impurity has tested positive in an adequately conducted Ames test.

GLP Inspection: Positive controls were not made fresh and some of the positive controls used were expired at the time of the study.

- 21 CFR 58.83: Reagents and solutions

"All reagents and solutions in the laboratory areas shall be labeled to indicate identity, titer or concentration, storage requirements, and expiration date. Deteriorated or outdated reagents and solutions shall not be used."

Ames study



Case Study 3: Data Repetition

Ames study submitted to address the potential mutagenicity of an impurity in a drug substance DMF referenced by eight different pending and approved ANDAs

Strain TA 1535 Experiment 1	Dose µg/plate	S9	Individual Colony Counts		
Test article	5000	-	420	410	412
		+	404	412	414
	1500	-	412	406	416
		+	416	410	420
	500	-	418	406	408
		+	428	416	418
	250	-	400	404	404
		+	412	406	416
	50	-	408	414	408
		+	410	416	410

Strain TA 1535 Experiment 2	Dose µg/plate	S9	Individual Colony Counts		
Test article	5000	-	420	410	412
		+	404	412	414
	1500	-	412	416	406
		+	416	410	420
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Initial review noted that there were unusual patterns in the colony count numbers

- Repeated colony count values between experimental repeats
- All even number colony counts

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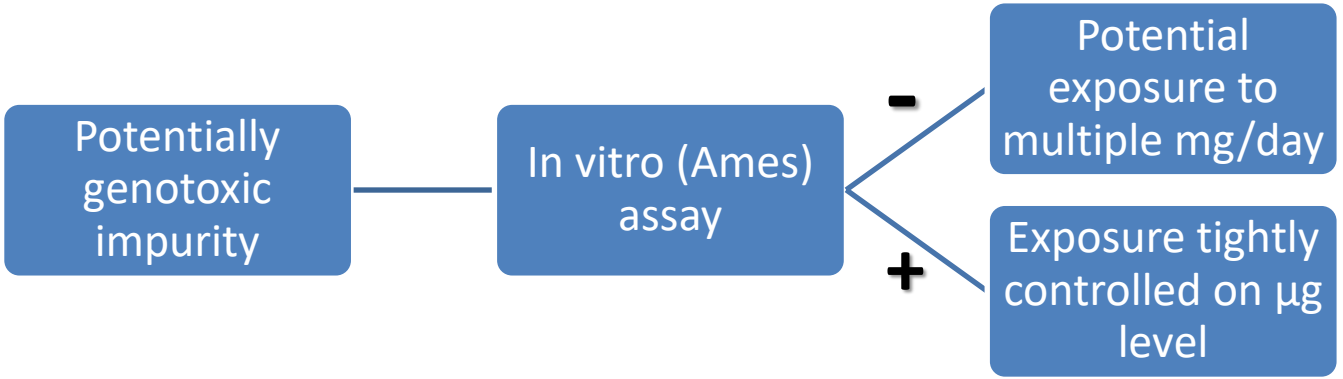
GLP Inspection

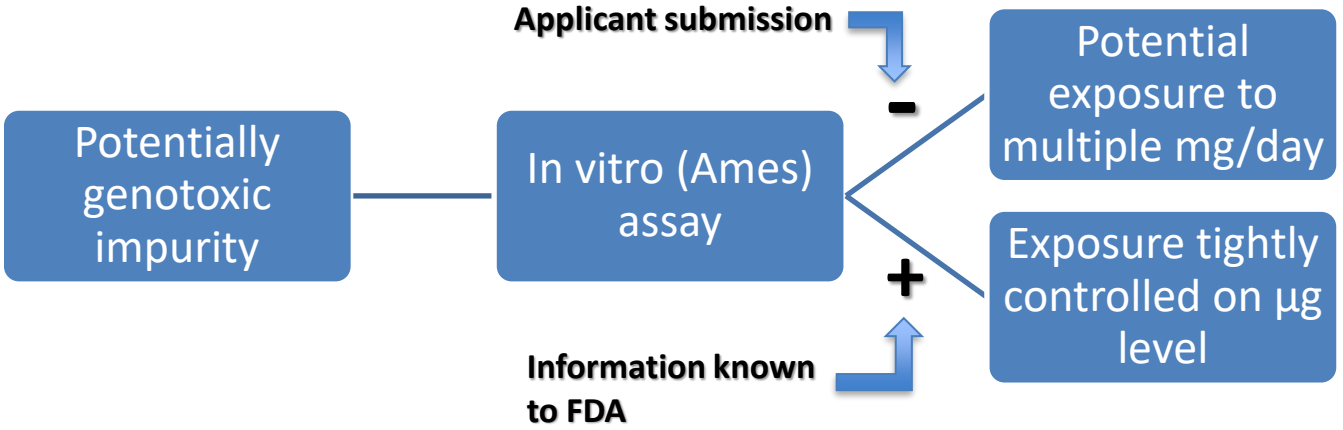
- Study director failed to assure that all experimental data were accurately recorded and verified [21 CFR 58.33(b)]
- Even number colony counts was due to standard operating procedure deviation that was not documented in the raw data nor authorized by the study director [21 CFR 58.81(a)]

What is the impact of a nonclinical study?



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

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



Data integrity issues could result in patient exposure to unsafe levels of an impurity

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
- Nonclinical study quality is of utmost importance
  - Review conclusions can determine patient exposure to an impurity
  - Review conclusions can have a broad impact
  - Major deficiency issued when data integrity issue arises

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 Many nonclinical studies are submitted with a statement that they are conducted in a GLP environment, however this does not necessarily mean that the study data are reliable.

Acknowledgements

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