Impurity Case Studies: Control of Potential Genotoxic Impurities in DMF

Hongbiao Liao
Division of Life Cycle API
Office of New Drug Products
Office of Pharmaceutical Quality
CDER/FDA

Generic Drug Forum
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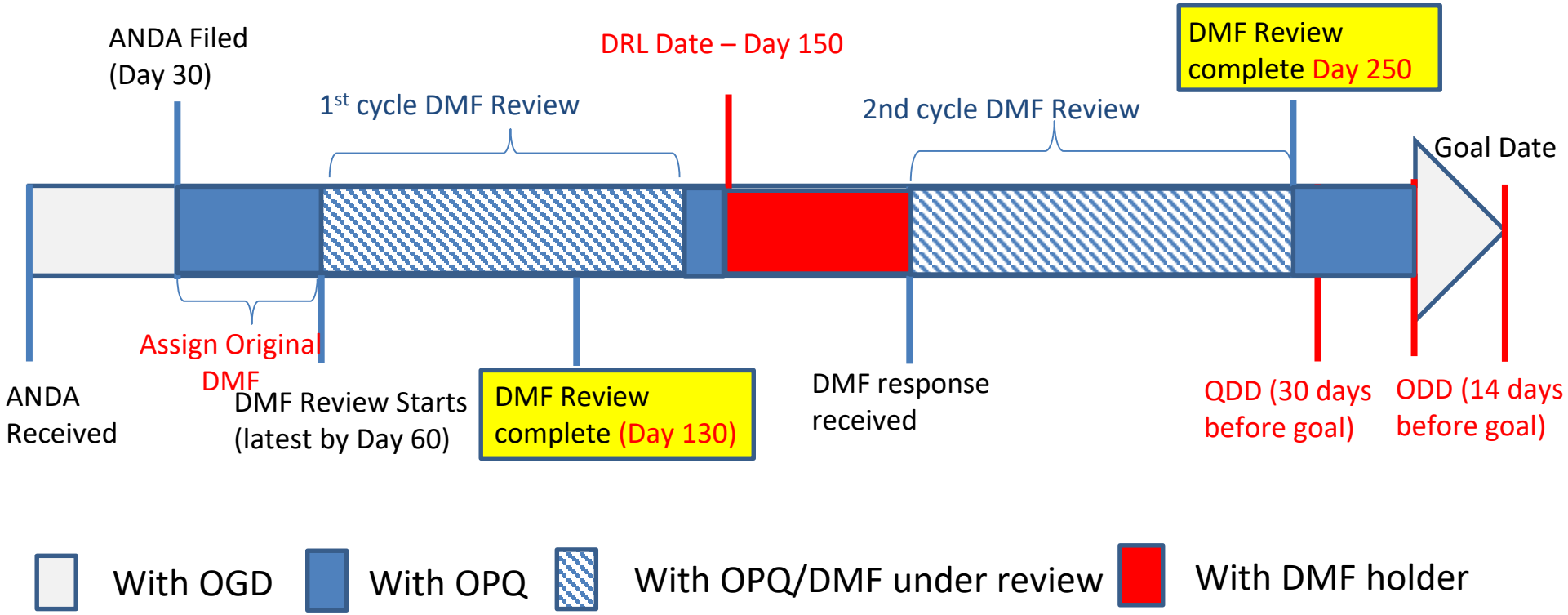
DMF Assignment Under GDUFA 2



- In a 10-month review clock, DMF assessment has about 7-month to complete.
- The typical response time by DMF holder is 2 to 3-month. Response in a timely way may allow for a second cycle assessment.

DMF Major Deficiencies

a. Inadequate selection or justification of starting materials

b. Toxicological studies needed to qualify an impurity

c. Reference to an inadequate secondary DMF which has not been assessed, or requires significant additional manufacturing information

d. Failure to provide adequate analytical procedures or method validation

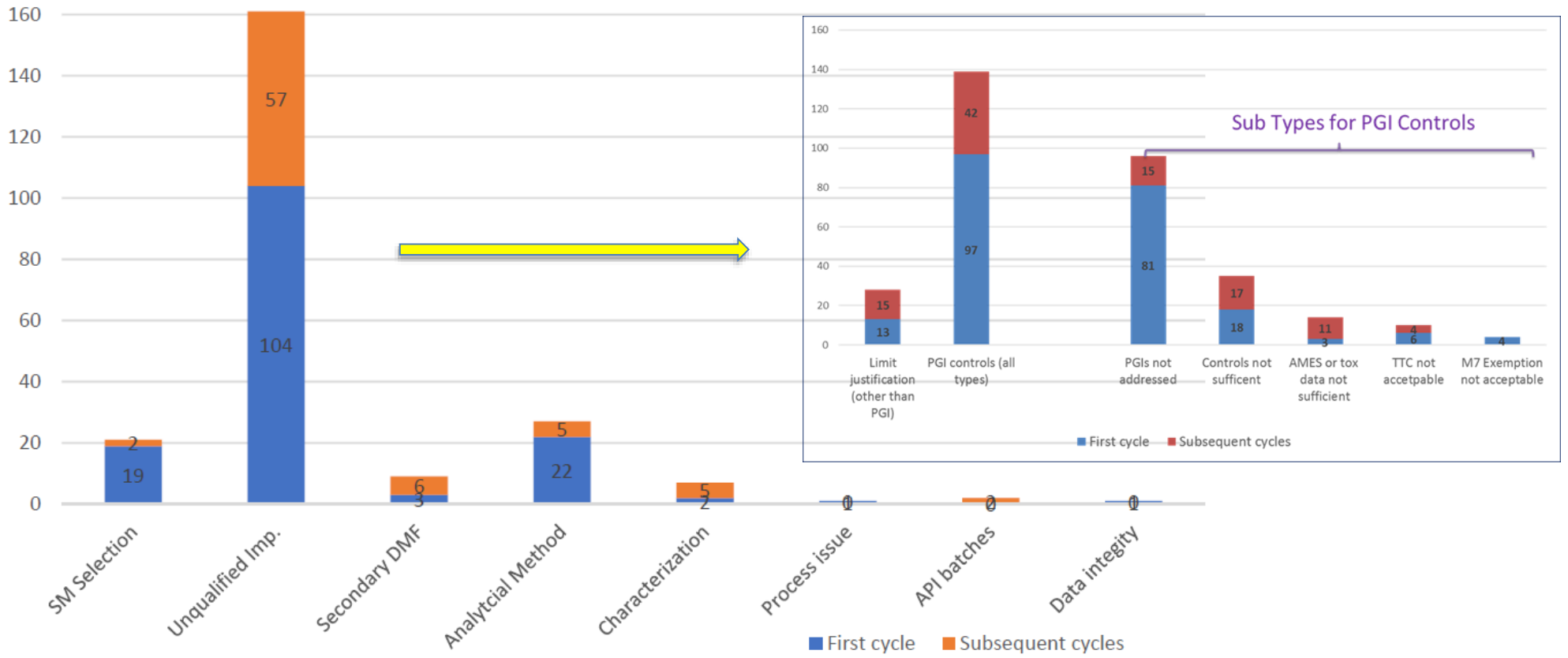
e. Insufficient physical or chemical characterization of drug substance, especially for complex active pharmaceutical ingredients (APIs)

f. Major change in drug substance manufacturing process

g. API batch inadequacies that require manufacture of a new API batch

Amendments to ANDA under GDUFA, Guidance for Industry, July **2018**

Deficiencies for PGI Controls



- DLAPI established a database since 10/2017. As of 10/2018, over 30% of DMFs have major deficiencies in the first review cycle.
- The main sub-category is qualification of impurities. Control and qualification for PGIs is the main reason for major deficiencies in DMFs.

Key Concept in ICH M7 - TTC

- TTC (Threshold of Toxicological Concern). TTC is developed to define an acceptable intake **for DNA reactive substances that have the potential to cause cancer**. High potency mutagenic carcinogens are controlled at/below compound specific acceptable limit.
- TTC calculation
  - **Acceptable intake** and **MDD** (Maximum Daily Dosage)
- Treatment duration for applying acceptable intake
  - Treatment duration should be located in RLD label. Alternatively, refer to treatment durations based on clinical use scenarios (ICH M7, Note 7)
  - Following are acceptable intakes for an Individual Impurity. Acceptable intakes for multiple impurities are slightly different.

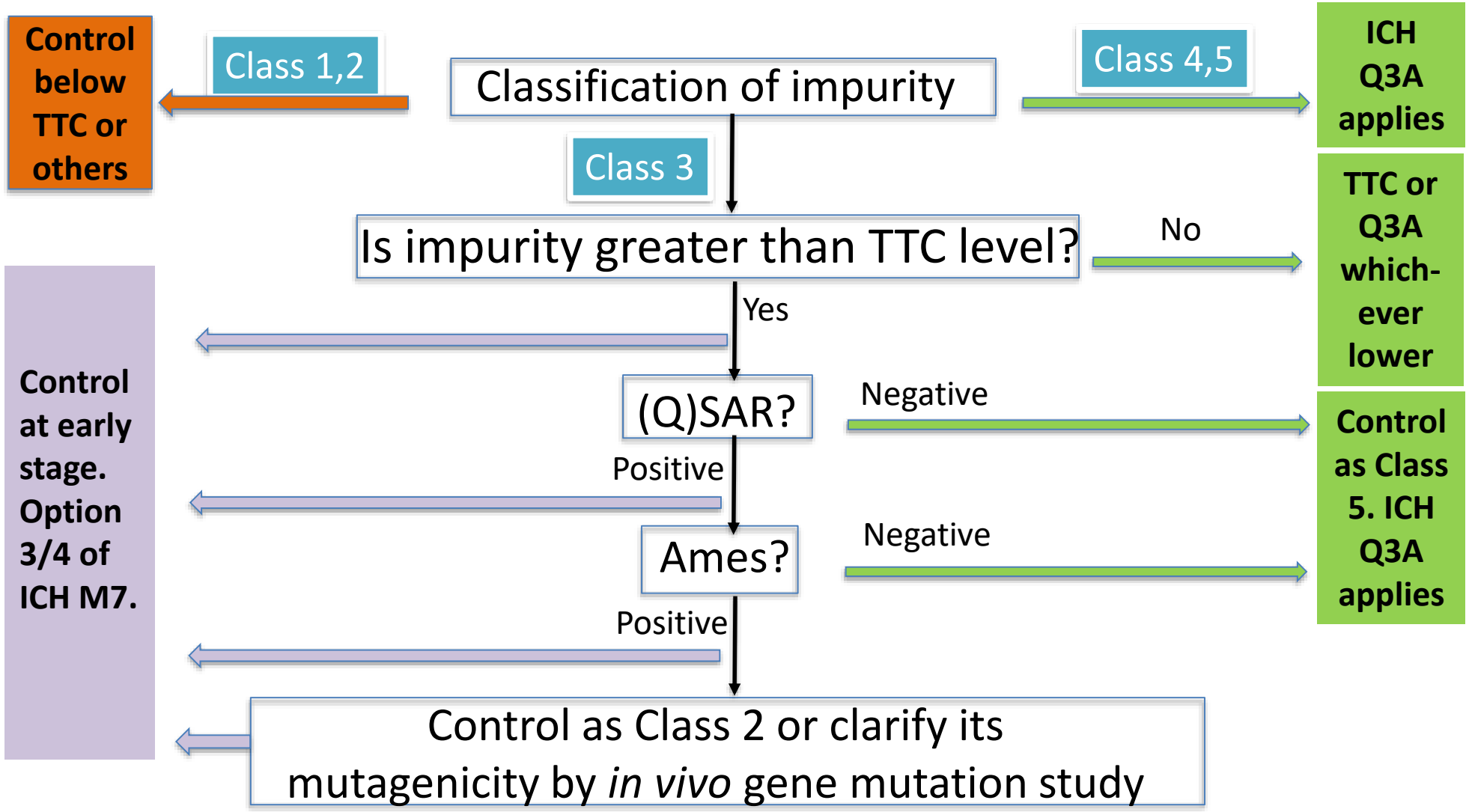
Duration of treatment	≤ 1 month	>1 - 12 months	>1 - 10 years	>10 years to lifetime
Daily intake [µg/day]	120	20	10	1.5

ICH M7 Classification of Impurities

Class	Definition
1	Known mutagenic carcinogens
2	Known mutagens with unknown carcinogenic potential (bacterial mutagenicity positive*, no rodent carcinogenicity data)
3	**Alerting structure, unrelated to the structure of the drug substance; no mutagenicity data**
4	Alerting structure, same alert in drug substance or compounds related to the drug substance (e.g., process intermediates) which have been tested and are non-mutagenic
5	No structural alerts, or alerting structure with sufficient data to demonstrate lack of mutagenicity or carcinogenicity

*Or other relevant positive mutagenicity data indicative of DNA-reactivity related induction of gene mutations

Decision Tree for Impurity Qualification



- Compendial specified impurity overrides the structural alert alone unless it is a known GI or a structural alert of very high concern (N-nitroso, aflatoxin-like and azoxy compounds).

Control Options (ICH M7 8.1)

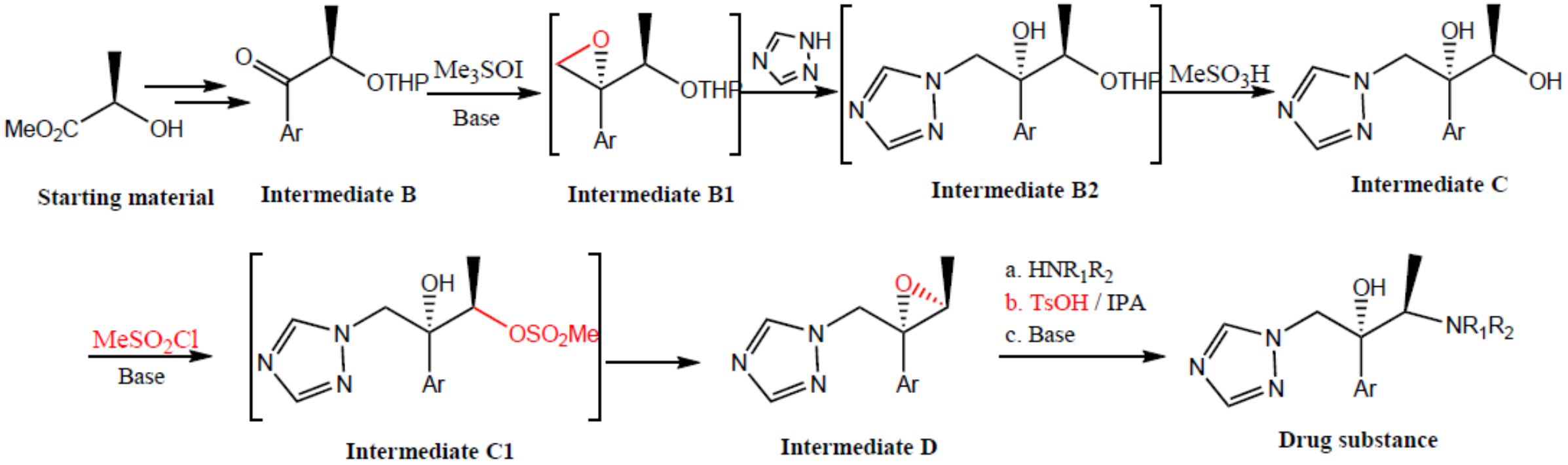
- Option 1: Monitor the impurity in the drug substance
  - Acceptance criterion at/below the TTC.
- Option 2: Monitor the impurity in intermediate, starting material or in-process control
  - Acceptance criterion at/below the TTC
- Option 3: Monitor the impurity in intermediate, starting material or in-process control
  - Acceptance criterion above the TTC, with demonstrated understanding of fate and **spike/purge** and associated process controls
- Option 4*: Design robust process controls to reduce the risk of impurity level above the TTC to negligible
  - The risk assessment might be provided as an estimated **purge factor** for clearance of the impurity by the process.

*Regulatory Toxicology and Pharmacology, *90* (**2017**), 22-28; OPRD, **2010**, *14*, 943-945

Reviewer's Checklist

Stage	Reviewer's checklist
Prior to assessment	1. Confirm whether M7 exemption applicable 2. Locate Treatment duration and MDD in RLD label 3. Identify Acceptable intakes and calculate TTC
Assessment	1. Identify alerting structures based on synthetic route 2. Search internal (Q)SAR database and submit internal (Q)SAR request 3. Submit Pharm/Tox consult if Ames test report provided (***3 months***). 4. Submit ComTox consult if (Q)SAR report provided (***2 weeks***). 5. If Control Options of ICH M7 adopted, ***assessment is Immediate***.
Conclusion	1. Conclude the assessment and cite appropriate deficiency

Case Study: Synthetic Route



- The above synthetic route is extracted from literature: Organic Process Research & Development, **2009**, *13*, 716–728 for Synthesis of Intermediate D; EP 3112360A for Synthesis of drug substance.

Recommended Control Options

PGI	Source	Proposed Control Strategy
Intermediate B1	*In-situ* intermediate	Option 4, Purging factor
Intermediate C1	*In-situ* intermediate	Option 3, IPC, Spike/Purge
Intermediate D	Isolated intermediate	Predicted to be negative for bacterial mutagenicity by (Q)SAR.
Methanesulfonyl chloride	Reagent	Option 4, Scientific justification
Isopropyl toluenesulfonate	Might form under harsh condition.	Option 1, Below TTC

- Without compromising drug substance quality, select best control option to minimize assessment time.

What Can Industry Improve?

Sub-type of PGI-related deficiencies	Recommendation
PGI not addressed	Provide a **complete list** of PGIs from reagents/starting materials/*in-situ* or isolated intermediates/by-product through simple comparison with a known alerting functionality, and through searches of published information such as CCRIS.
Control not sufficient	For Option 3, Acceptance criterion above the TTC, demonstrate process capability at the proposed level with spike/purge data.
Ames or (Q)SAR data not sufficient	**Quality data** of AMES test, which can be performed per ICH S2(R1) and OECD 471 Bacterial Reverse Mutation test (Ames test). **Quality data** of (Q)SAR*, from ICH M7 compliant software.
TTC not acceptable	Calculate with MDD and Acceptable intakes per RLD information.
M7 exemption not acceptable	M7 Exemption applies to drug substance and drug product intended for advanced cancer indications; or, drug substance itself genotoxic **at therapeutic concentrations**.

*Regulatory Toxicology and Pharmacology, *73* (**2015**), 367-377; *77* (**2016**), 13-24

Impact of Post-Approval Changes

- Post-approval submissions involving the drug substance CMC should include an evaluation of the potential impact associated with mutagenic impurities due to changes of the route of synthesis, reagents, solvents, or process conditions after the starting material.
- Specifically, changes should be evaluated to determine if the changes result in any new mutagenic impurities or higher acceptance criteria for existing mutagenic impurities.
- Valsartan-related recall occurred in 07/2018 due to the presence of N-Nitrosodimethylamine (NDMA) in API. If a manufacturer detects new or higher levels of impurity, action should be taken to prevent changes to the product's safety profile.

Summary

- Control of PGIs is one of the main reason for major deficiencies in DMFs. Following ICH M7 step-by-step could make control of PGIs right the first time.

- In-depth understanding the formation, fate, and purge will facilitate selection of appropriate control strategy. This will reduce the assessment time and increase the chance that the DMF will become adequate within ANDA first-cycle review clock.

- Compliance with ICH M7 is required in post-approval submission. See ICH M7 Appendix 1 for the applicable scope scenarios.

Acknowledgement

- David Skanchy
- Ramnarayan S. Randad
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Thank you

Please send comments to DMFOGD@fda.hhs.gov

Pharmacology/Toxicology Impurity Case Studies

Victoria Keck, MS, VMD

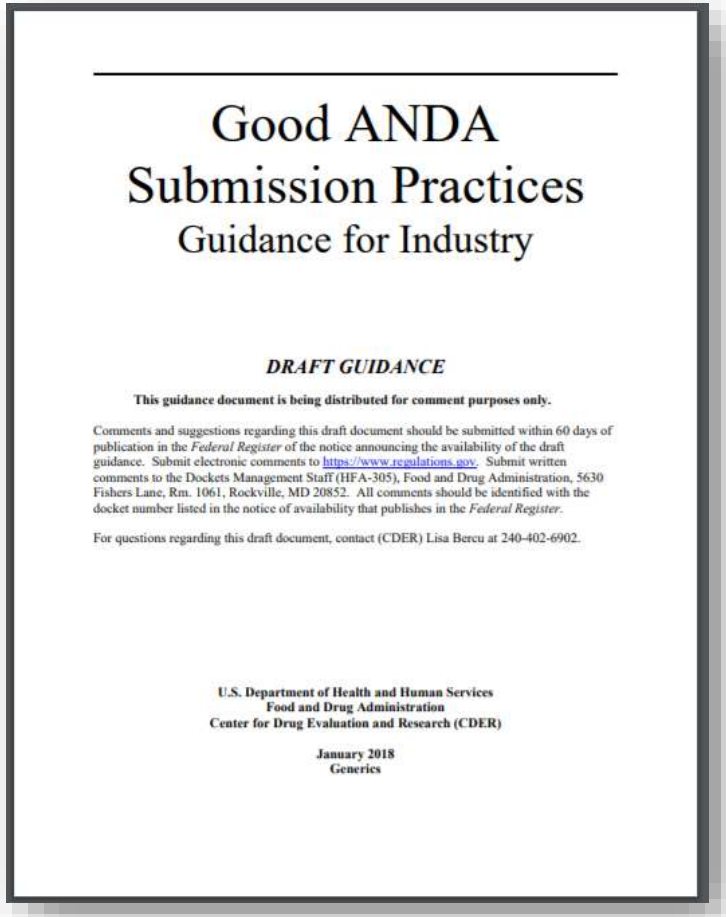
Toxicologist

Division of Clinical Review

Office of Generic Drugs

Center for Drug Evaluation and Research
U.S. Food and Drug Administration

Pharmacology/Toxicology Case Studies



Good ANDA
Submission Practices
Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (CDER) Lisa Bercu at 240-402-6902.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

January 2018
Generics

https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm591134.pdf

Pharmacology/Toxicology Case Studies

Generic formulation safety review

- Expected to have same safety profile as the RLD
- Impurity profile should not pose a greater risk than RLD

ICH and FDA guidances are key resources

- ICH M7: Mutagenic impurities
- ICH Q3A: Impurities in Drug Substances
- ICH Q3B: Impurities in Drug Products
- FDA Good ANDA Submission Practices

https://www.ich.org/home.html

Case 1: Use of *in silico* methods to characterize safety of an impurity

Case 1: Impurity Safety Characterization

Drug substance (DMF)

- ANDA with oral, chronic-use indication
- Maximum daily dose is 1000 mg

Impurity A exceeds ICH Q3A limits

- Proposes limit of NMT 0.5% (5 mg/day)

ICH M7 Mutagenic Impurities

Duration of treatment	≤ 1 month	>1 - 12 months	>1 - 10 years	>10 years to lifetime
Daily intake [µg/day]	120	20	10	1.5

ICH Q3A Drug Substance Impurities

Maximum Daily Dose[1]	Reporting Threshold[2,3]	Identification Threshold[3]	Qualification Threshold[3]
≤ 2g/day	0.05%	0.10% or 1.0 mg per day intake (whichever is lower)	0.15% or 1.0 mg per day intake (whichever is lower)
> 2g/day	0.03%	0.05%	0.05%

Case 1: Impurity Safety Characterization

Applicant submitted *in silico* prediction ((Q)SAR) to address:

- Mutagenicity
- Carcinogenicity
- Reproductive and developmental toxicity
- Liver and cardiovascular effects

When are *in silico* methods adequate for characterizing the safety of an impurity?

Check: Good ANDA Submission Practices Guidance

Case 1: Impurity Safety Characterization

When are *in silico* methods **adequate**?

- Bacterial **mutagenicity** prediction of an impurity (Q)SAR
  - Submit one **expert-based** and one **statistical-based** model
  - Submit full study reports
  - See ICH M7 guidance

Common pitfalls of (Q)SAR submissions:

- Single model submitted
- Insufficient information on model validation
- Full study report not submitted

Side note: Cramer Classification is insufficient to characterize safety

Case 1: Impurity Safety Characterization

When are *in silico* methods **not** adequate?

- General toxicity
  - Not validated for the endpoints of general toxicity studies

What is acceptable for addressing general toxicity?

- Repeat dose general toxicology (full reports)
- Published literature (provide article)

Case 1: Impurity Safety Characterization

Drug substance (DMF) referenced by ANDA with oral, chronic use indication

Maximum daily intake of Impurity A exceeds ICH Q3A qualification threshold

Applicant submitted *in silico* prediction ((Q)SAR) to address:

- Mutagenicity
  - Full study report, one expert-based and one statistical-based method
  - May control up to ICH Q3A limits
- Carcinogenicity
- Reproductive and developmental toxicity
- Liver and cardiovascular effects

Case 1: Impurity Safety Characterization

Drug substance (DMF) referenced by ANDA with oral, chronic use indication

Maximum daily intake of Impurity A exceeds ICH Q3A qualification threshold

Applicant submitted *in silico* prediction ((Q)SAR) to address:

- Mutagenicity
  - Full study report, one expert-based and one statistical-based method
  - May control up to ICH Q3A limits

To characterize safety of impurity above ICH Q3A limit

Provide repeat dose toxicology study covering context of use and/or published literature

OR

Conduct comparative impurity analysis with RLD

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Case 2: Metabolite justification to control an impurity above ICH limits

Case 2: Metabolite Justification

ICH Q3B Drug Product Impurities

Qualification Thresholds

Maximum Daily Dose[1]	Threshold[2,3]
< 10 mg	1.0% or 50 µg TDI, whichever is lower
10 mg - 100 mg	0.5% or 200 µg TDI, whichever is lower
>100 mg - 2 g	0.2% or 3 mg TDI, whichever is lower
> 2 g	0.15%

ANDA for oral drug product

- Maximum daily dose is 1000 mg

Impurity B exceeds ICH Q3B qualification threshold

- Proposes limit of 3% (30 mg/day) and ICH Q3B limit is 0.2% (2 mg/day)

Case 2: Metabolite Justification

Applicant submitted metabolite justification using public literature

- Claims Impurity B is metabolite of the active pharmaceutical ingredient

Is this justification adequate?

Check: Good ANDA Submission Practices Guidance

Case 2: Metabolite Justification

Is this justification adequate?

- Published literature: Impurity is a metabolite detected in rodent and human urine
  - There is no quantitative information about systemic exposure
  - Inadequate information to support metabolite argument

What is an adequate justification?

- Quantitative information on systemic exposure
  - Plasma levels that equals or exceeds the proposed clinical exposure levels
  - Demonstrate systemic exposure is at a level to support impurity limit

Case 2: Metabolite Justification

ANDA Complete Response Amendment

- Supplied data to show significant levels of Impurity B were in the plasma samples in their bioequivalence study
  - Metabolite was present in both test and reference (RLD) samples
  - Presence was not a result of degradation
  - Data on plasma levels was sufficient to qualify the level of 3% Impurity B

Case 2: Metabolite Justification

ANDA for oral drug product with maximum daily dose of 1000 mg

Impurity B exceeds ICH Q3B qualification threshold

- Proposes limit of 3% (30 mg/day) and ICH Q3B limit is 0.2% (2 mg/day)

Applicant submitted metabolite justification using public literature

- Claimed Impurity B is metabolite of the active pharmaceutical ingredient
- No quantitative information on systemic exposure → Complete Response

Ways to characterize safety with metabolite justification

- Published literature, conduct nonclinical study, or look at BE samples

Summary

Pharmacology/Toxicology evaluates the safety of generics

- Safety of impurity profiles are major area of focus
- ICH and FDA guidances are key resources

Two case studies to illustrate common reasons for deficiencies

- In silico predictions to inform safety of impurity above ICH limits
  - ✓ Mutagenicity: Two in silico methods (submit full report)
  - ✓ General Toxicity: in silico not validated, instead submit repeat-dose general toxicity studies or published literature (submit full reports and copies of articles)
  - ✓ Do not rely on Cramer Classification
- Metabolite justification to inform safety of impurity above ICH limits
  - ✓ Provide data to demonstrate systemic exposure as a metabolite justifies level of impurity


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