Drug Substance Postapproval Changes Guidance: Determination of Impurity Profile Equivalence

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Postapproval Changes to Drug Substances

- Draft Guidance for Industry published 09/10/2018
- Category: Drugs; Subcategory: Pharmaceutical Quality/CMC
- Focuses on changes to drug substance manufacturing during the drug product application's postapproval period
- Addresses how the risk of changes to the drug substance should be assessed
- Includes recommendations regarding the documentation needed to support changes

Scope

- Applies to synthetic drug substances and the synthetic steps involved in preparing semisynthetic drug substances, including:
  - Facility, scale, and equipment changes associated with all steps of drug substance manufacturing
  - Specification changes to starting materials, raw materials, intermediates, and the unfinished and final drug substance
  - Synthetic manufacturing process changes
  - Changes to the source of the drug substance
  - Changes to the container closure system for the drug substance

Out-of-Scope

The guidance does not apply to postapproval changes to:

- Peptides
- Oligonucleotides
- Radiopharmaceuticals
- Drug substances isolated from natural sources
- Drug substances produced by procedures involving biotechnology
- Nonsynthetic steps (such as fermentation) for semisynthetic drug substances
- Complex active ingredients, as defined in the GDUFA-II Commitment Letter

Assessment of Risk

- Any modification to drug substance manufacturing carries some risk of causing an adverse impact on quality.
- Each drug substance manufacturer should assess the particular proposed modification to their drug substance to determine the risk associated with the change.
    - Certain modifications (e.g., equipment changes) are viewed as less likely to result in an adverse impact than others (e.g., changes in the synthetic route)
    - Late-stage changes in the drug substance manufacturing process are generally viewed as more likely to have an adverse impact on the quality of the drug substance and, consequently, on the drug product.

Assessment of Risk

Central Principle: a change in the drug substance manufacturing process can be adequately assessed by comparing three consecutive pilot or commercial scale batches of pre- and post- modification material

Evaluation may include:

- A comparison of impurities in pre- and post-modification intermediates, the unfinished drug substance, and/or the drug substance
- A comparison of the drug substance's physical properties before and after modification
- Drug substance stability data

Impurity Profile Evaluation

If the impurity profile of an isolated material (i.e., isolated intermediate, unfinished drug substance, or drug substance) following the change is equivalent to that of pre-change material, the drug substance's impurity profile is considered unaffected by the modification.

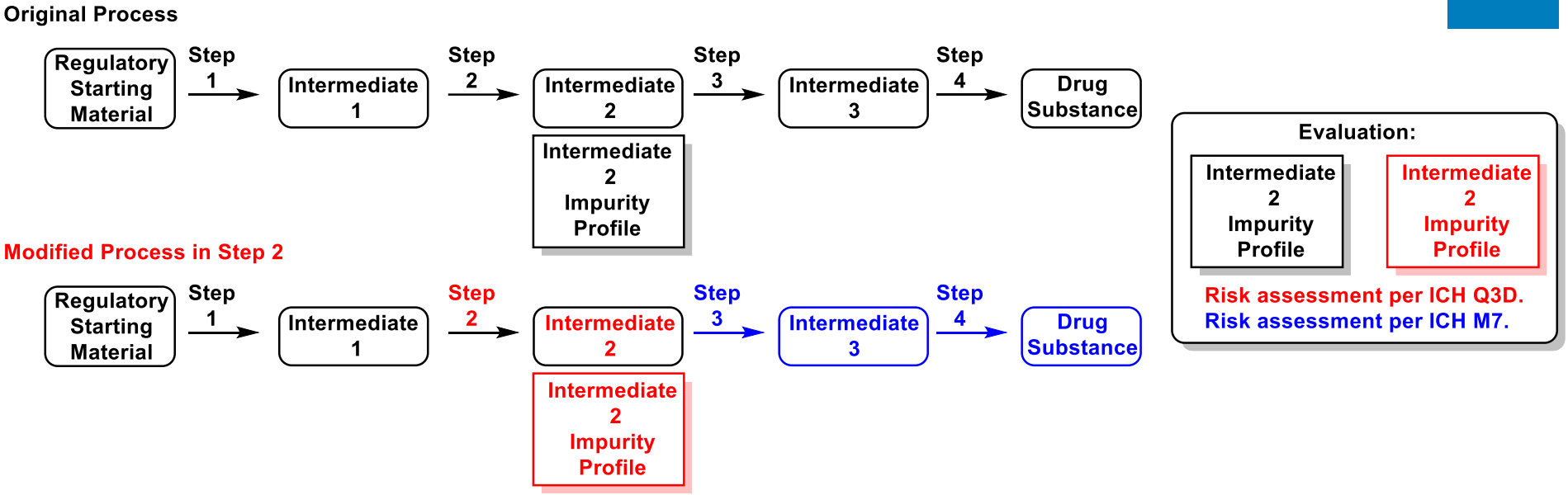
- Determine the stage in the manufacturing process at which impurities should be evaluated.
- Determine levels of existing and new organic impurities (ICH Q3A), residual solvents (ICH Q3C) and inorganic substances (ICH Q3D).
- Determine the potential for the formation of mutagenic and unusually toxic impurities, including nitrosamines (ICH M7, FDA's Guidance: Control of Nitrosamine Impurities in Human Drugs).
- Establish the adequacy of the analytical procedures used for the above purposes.

Impurity Profile Evaluation

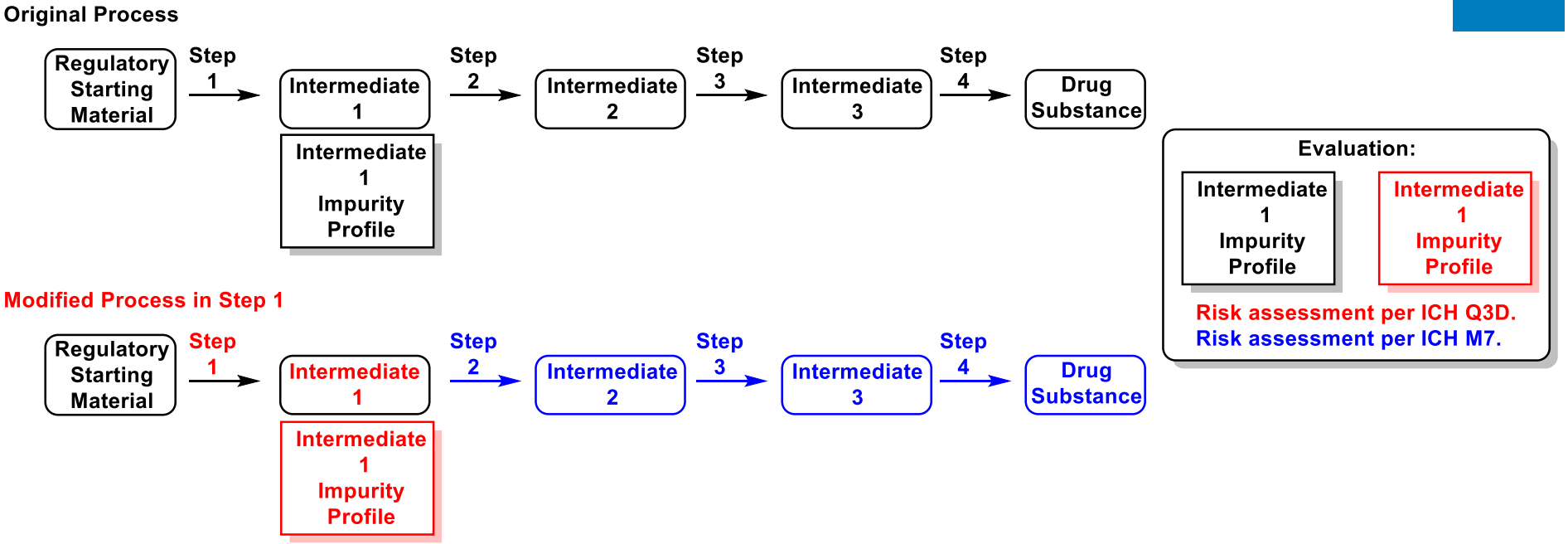
If the manufacturing modification occurs at an upstream step before the final intermediate is produced, and equivalence cannot be demonstrated for the intermediate isolated immediately following the change, the impurity search should be extended to the next downstream intermediate.

The impurity search should also be expanded to include appropriate downstream impurities that may be formed during the manufacturing process. The evaluation process should be repeated on downstream intermediates up to and including the drug substance, if necessary.

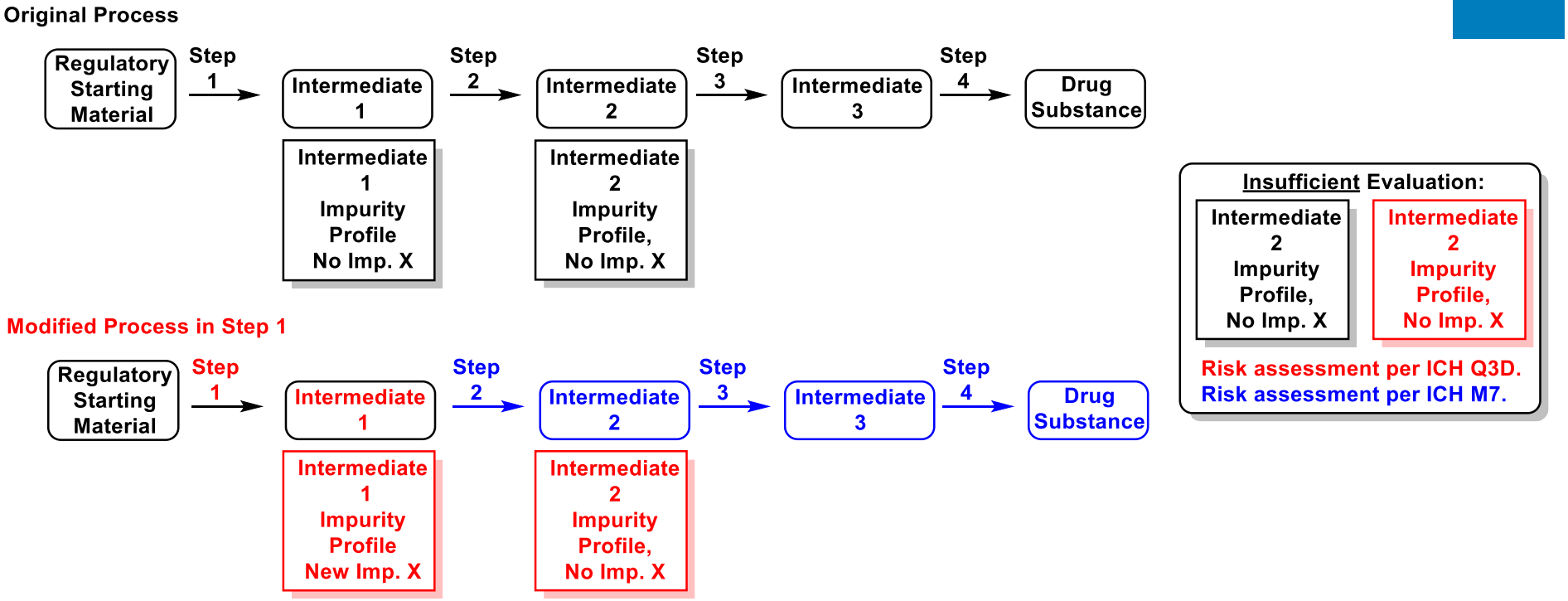
Impurity Profile Evaluation: Example 1



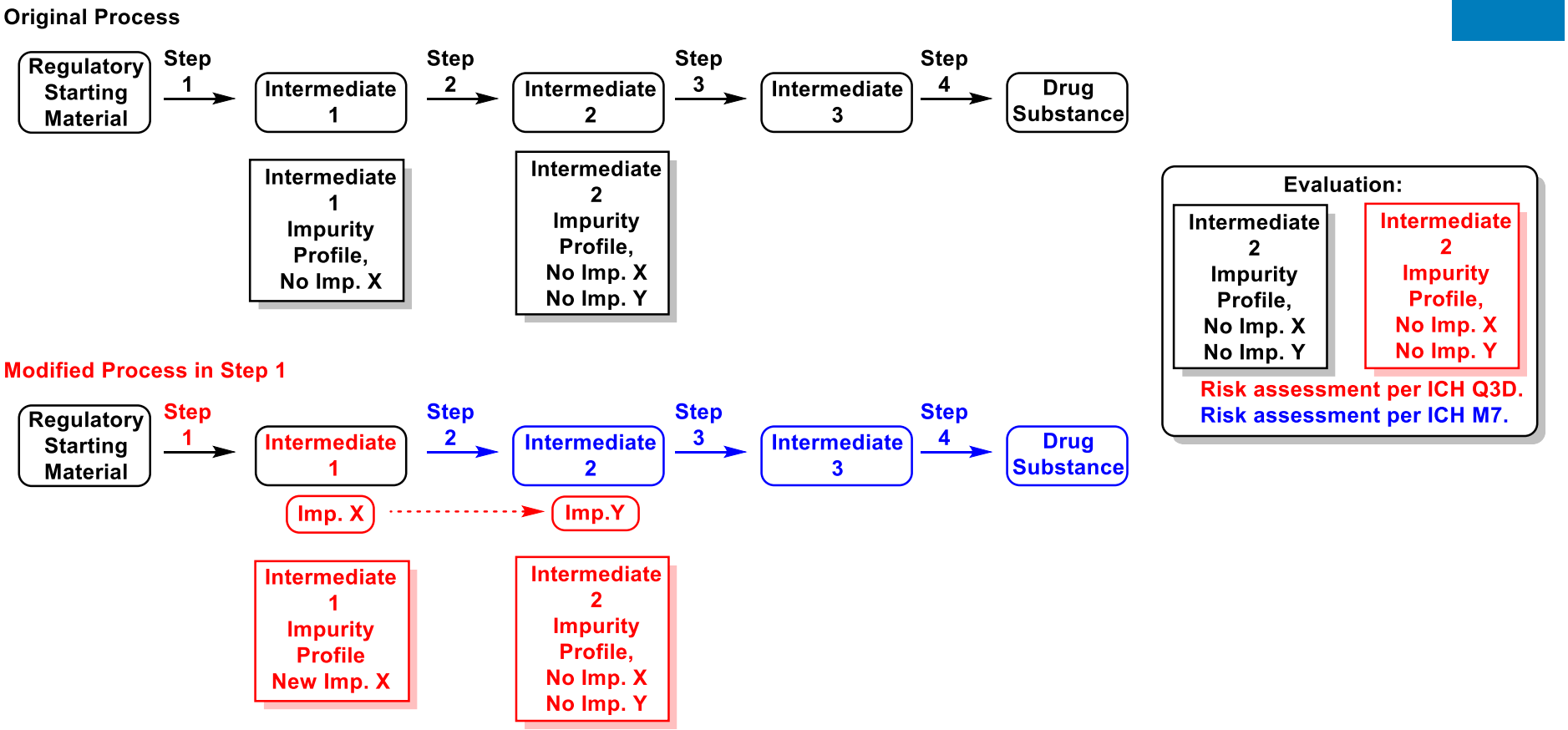
Impurity Profile Evaluation: Example 2



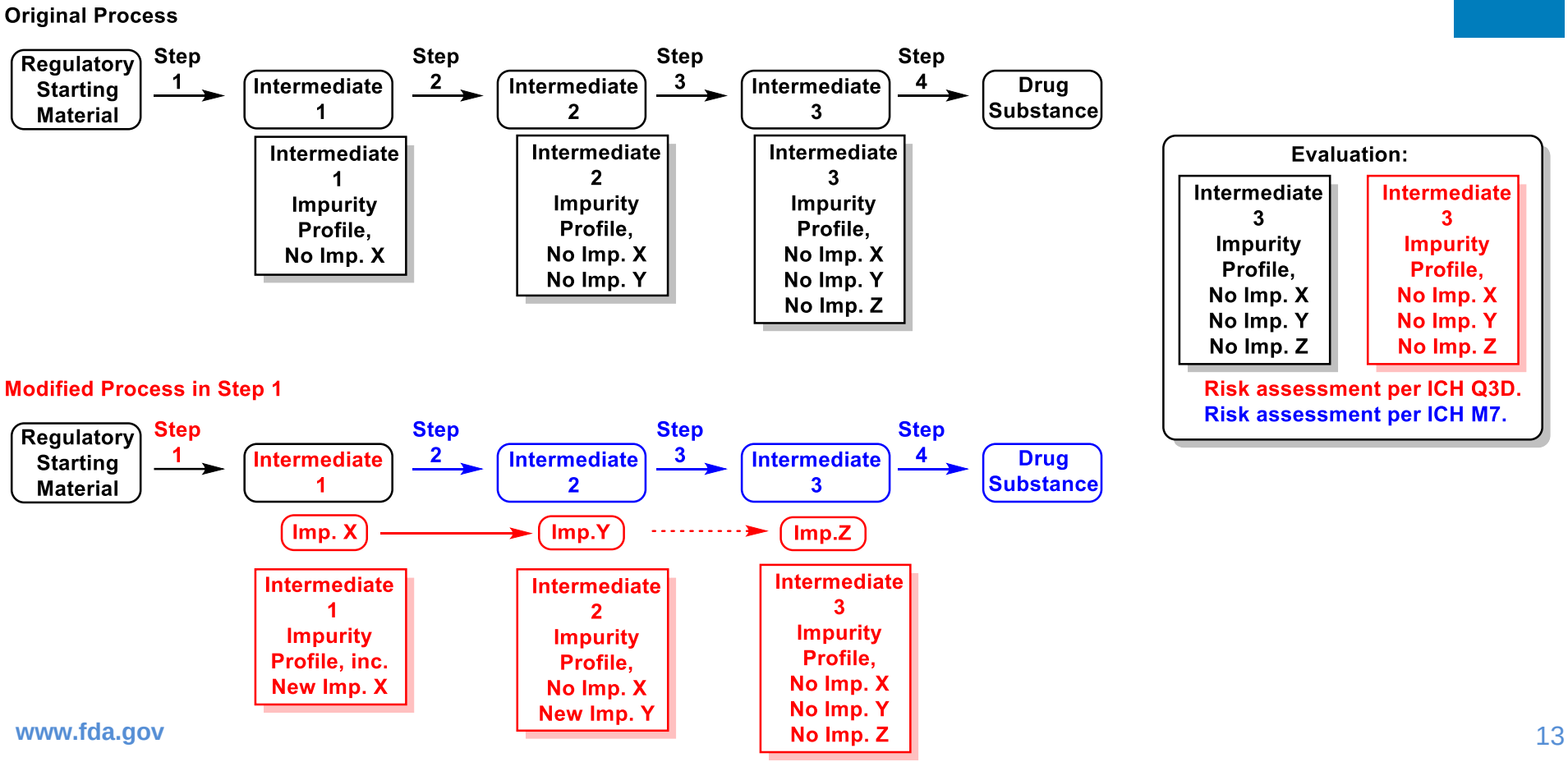
Impurity Profile Evaluation: Example 3



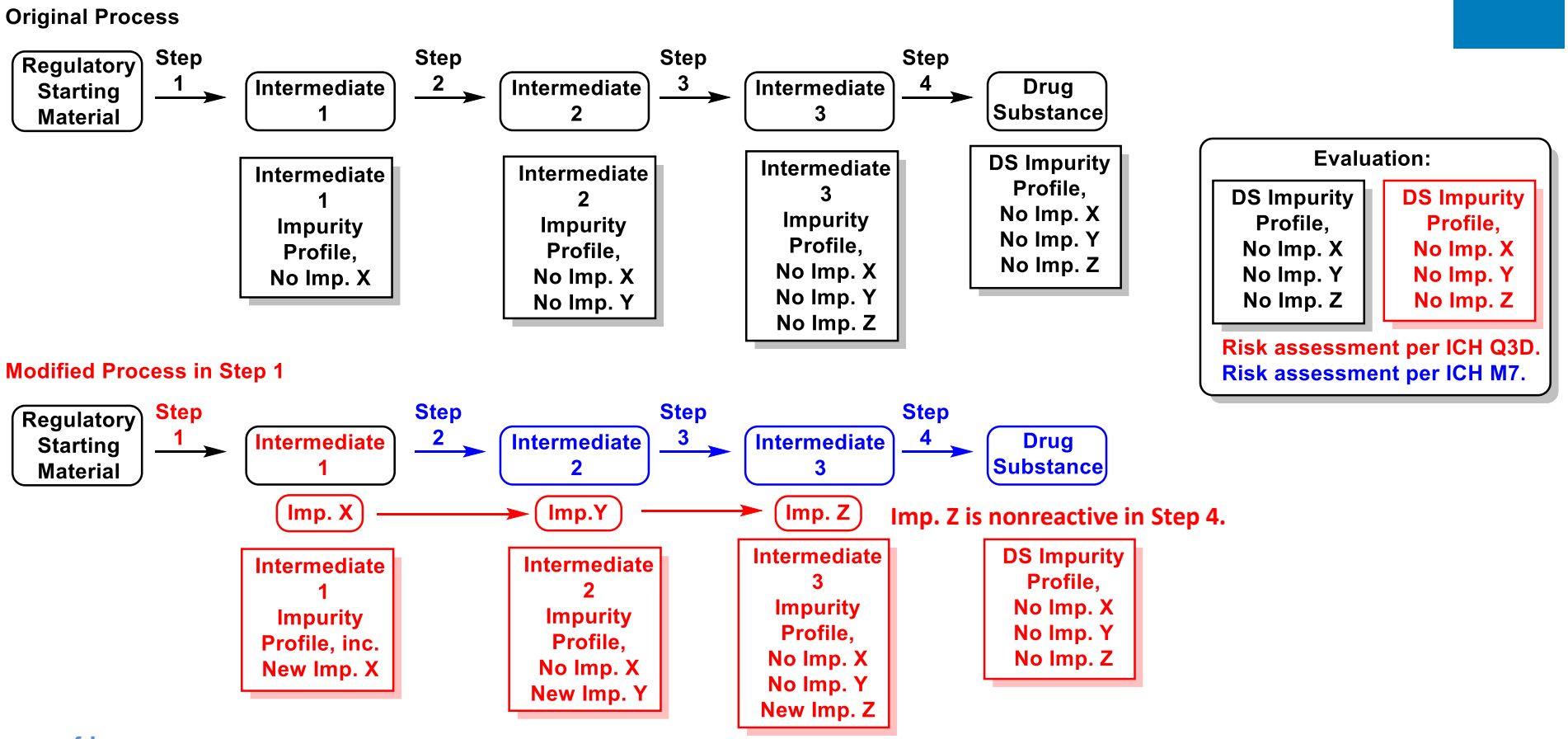
Impurity Profile Evaluation: Example 4



Impurity Profile Evaluation: Example 5



Impurity Profile Evaluation: Example 6



Impurity Profile (non)Equivalence

- Impurity profile equivalence is not a requirement.
- Consider modifying impurity tests in one or more specifications:
  - Raw material, intermediate and drug substance specification changes
  - Proposed acceptance criteria should be justified (e.g. spike/purge study data)
  - Downstream analog impurity control
  - Downstream reagent or solvent reactivity leading to mutagenic impurities
  - Updated batch analyses or COAs
  - Supporting method validation/verification, if necessary
  - See Guidance Section VII, page 21 (Specification Changes)

Summary

- Each drug substance manufacturer should assess the particular proposed modification(s) to determine the risk associated with the change(s).
- The Guidance provides recommendations on carrying out this risk assessment.
  - Other approaches may be acceptable.
- Impurity profile equivalence determination of intermediates and drug substances is a popular route taken to assess the risk associated with changes.
- Impurity profile equivalence is not a requirement.
- Impurity profile equivalence should be complete.
  - Comprehensive evaluation of potential impurities (reagents, solvents, byproducts, both inorganic and organic, including mutagenic impurities)
  - Occur at the correct point(s) in the process for the impurities being evaluated

Resources

- FDA Draft Guidance for Industry, Sept 2018: Postapproval Changes to Drug Substances
  - www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM619947.pdf
- ICH Q3A, Impurities in New Drug Substances (www.ich.org/page/quality-guidelines)
- ICH Q3C, Impurities: Guideline for Residual Solvents
- ICH Q3D, Guideline for Elemental Impurities
- ICH M7, Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk
- FDA Guidance for Industry, Sept 2020: Control of Nitrosamine Impurities in Human Drugs
  - www.fda.gov/regulatory-information/search-fda-guidance-documents/control-nitrosamine-impurities-human-drugs
- GDUFA-II Commitment Letter
  - www.fda.gov/industry/generic-drug-user-fee-amendments/submission-review

Questions

- Please type questions regarding the content of this presentation into the "Q&A Box" in the bottom right of your screen so that they can be addressed during the panel Q&A session scheduled immediately after this presentation.

- Additionally, you may send questions regarding this presentation to DMFWorkshop2021@fda.hhs.gov by 03/19/2021 for inclusion in the follow up webinar scheduled for April 9, 2021.