POLICY AND PROCEDURES

Office of Pharmaceutical Quality

Assessing Impurity Acceptance Criteria as Part of Specifications for NDAs, ANDAs, and BLAs Based on Clinical Relevance

Table of Contents

PURPOSE

This MAPP provides guiding principles and approaches for assessing drug substance and drug product impurity[1] acceptance criteria for non-mutagenic impurities in new drug applications (NDAs), abbreviated new drug applications (ANDAs), and biologics license applications (BLAs), based on the consideration of clinical relevance.[2]

While the ICH guidance for industry Q3A(R2) *Impurities In New Drug Substances* (June 2008) and the ICH guidance for industry Q3B(R2) *Impurities In New Drug Products* (August 2006)[3] apply to new drug substances produced by chemical synthesis and new drug products, the principles of these guidances and the principles of this MAPP may apply to other drug substances and drug products, including some semi-synthetic and fermentation products[4], and peptides,[5] submitted in NDAs and ANDAs.

[1] In this MAPP, impurity can refer to process- and product-related impurities including degradation products for drug substance and drug product.
[2] In this MAPP, clinically relevant acceptance criteria are defined as a set of acceptance ranges to which an impurity should conform in order for the product to be safe and effective when used as labeled.
[3] See the ICH guidance for industry *Q3A Impurities in New Drug Substances* (Rev. 2, June 2008) and the ICH guidance for industry *Q3B Impurities in New Drug Products* (Rev. 2, August 2006).
[4] See the draft guidance for industry Establishing Impurity Specifications for Antibiotics (April 2026). When final, this guidance will represent FDA's current thinking on this topic.
[5] ICH *Q3A(R2*) and *Q3B(R2)* exclude certain NDA and ANDA products (e.g., peptides, oligonucleotides, fermentation products, and semi-synthetic products).

The principles in this MAPP may also apply to:

- Establishment of acceptance criteria for DNA-reactive (i.e., mutagenic) impurities that are generally controlled at tighter limits according to the ICH guidance for industry *M7(R2) Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk* (April 2023).[6]

- Investigational drug substances and drug products, depending on the risk.

- Enantiomeric impurities, where the active ingredient is a single enantiomer.

The principles that guide the development of a specification can be impacted by the assessment of risk to safety and efficacy based on context of use as well as other factors, such as clinical experience. The context of use includes, but is not limited to, dosage forms, dosing regimens, route and duration of drug administration, clinical indications, and the intended patient populations (e.g., pediatric or geriatric populations). Therefore, an impurity acceptance criterion cannot be established by one definitive approach and instead should be established on a case-by-case basis.

The following are excluded from this MAPP:

- Residual solvents and elemental impurities, as these are addressed in the ICH guidance for industry *Q3C(R8) Impurities: Guideline for Residual Solvents* (April 2021) and the ICH guidance for industry *Q3D(R2) Guideline for Elemental Impurities* (April 2022). Refer to ICH Q3C(R8) and ICH Q3D(R2) for establishing limits for these impurities.

- Extraneous contaminants that should not occur in drug substances and drug products and are addressed by current Good Manufacturing Practices requirements (e.g., adventitious viral, bacterial, and mycoplasma contamination[7]).

- Microbiological attributes (e.g., endotoxin, microbial limits).

- Leachables from the container closure system.[8]

---

[6] See the ICH guidance for industry *M7 Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk* (July 2023), the guidance for industry *Control of Nitrosamine Impurities in Human Drugs* (September 2024) and the guidance for industry *Recommended Acceptable Intake Limits for Nitrosamine Drug Substance-Related Impurities* (August 2023). Cohort of concern compounds, such as nitrosamines (small molecules and nitrosamine drug substance-related impurities (NDSRIs)), should be controlled according to relevant guidance documents. ICH Q3A, Q3B, and M7 thresholds typically do not apply to cohort of concern compounds.

[7] See 21 CFR 211.113.

[8] See the guidance for industry *Container Closure Systems for Packaging Human Drugs and Biologics* (May 1999).

- Polymorphic forms.[9]

BACKGROUND

Impurity acceptance criteria are established to provide assurance that a product performs as intended. Currently, the establishment of a drug substance and drug product impurity acceptance criterion can be supported by clinical data, nonclinical data (e.g., in silico, in vitro, and animal data), comparative impurity analysis of the proposed drug product with an FDA approved drug product (e.g., listed drug or reference listed drug (RLD)), analytical precision of the method used to measure the impurity, and manufacturing process capability, as appropriate.

This MAPP provides recommendations to OPQ product quality assessors on the types of data and information as well as the limitations that can be used by applicants to establish impurity acceptance criteria. In general, the types of data and information should be guided by the consideration of clinical impact of impurity levels, as opposed to manufacturing process capability, to ensure the acceptance criteria are clinically relevant.

POLICY

1. The terminology described in ICH Q3A(R2), Q3B(R2), and the ICH guidance for industry Q6A *Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances* (December 2000) should generally be applied to NDA and ANDA products. Specifically, a specification should include the following:

   Drug Substance
   - Each specified identified impurity
   - Each specified unidentified impurity
   - Any unspecified impurity with an acceptance criterion of not more than (≤) the identification threshold
   - Total impurities

   Drug Product
   - Each specified identified degradation product
   - Each specified unidentified degradation product
   - Any unspecified degradation product with an acceptance criterion of not more than (≤) the identification threshold

[9] Refer to ICH Q6A for a discussion on when it is appropriate to set acceptance criteria for polymorphic forms.

- Total degradation products

2. For products submitted in NDAs and ANDAs where the applicant's proposed acceptance criteria are not more than the ICH Q3A(R2) or Q3B(R2) qualification threshold, an acceptable limit for a specified impurity in the drug substance and drug product can be proposed and established at the qualification threshold, provided there are no toxicological, immunological, or clinical concerns at this level. For impurities known to be unusually potent, toxic, or have immunological, pharmacological, or clinical concerns, the proposed acceptance criteria based solely on ICH Q3A(R2) and Q3B(R2) qualification threshold are not sufficient and need to be adequately justified.

    2.1. The acceptance criterion for total impurities excluding significant human metabolites,[10] generally, should not exceed the summation of acceptance criteria for individual specified (identified and unidentified) impurities and unspecified impurities.[11] Individual impurities that are also significant human metabolites should be considered separately. The sum total of all impurity acceptance criteria, including those for significant metabolites, should not exceed thresholds that may compromise product potency/assay through product expiry.

3. The proposed acceptance criteria should be justified for the following:

    (a) Products submitted in NDAs and ANDAs where the applicant's proposed acceptance criteria are greater than the ICH Q3A(R2) or Q3B(R2) qualification threshold.
    (b) Products submitted in NDAs and ANDAs that are excluded from ICH Q3A(R2) and Q3B(R2).[12]
    (c) Products submitted in BLAs.[13]

4. Nitrosamines (small molecules and nitrosamine drug substance-related impurities (NDSRIs)) may lack the carcinogenicity and mutagenicity study data from which an acceptable intake (AI) limit can be determined. By using the predicted carcinogenic potency categorization approach, manufacturers and applicants may use structural features of NDSRIs to generate a recommended AI limit. Manufacturers and

[10] ICH M3(R2) defines that significant human metabolite(s) are those that occur at exposures greater than 10 percent of total drug-related exposure.
[11] Total impurities acceptance criterion may be established based on the risk assessment and allowing normal analytical and manufacturing variation. The acceptability of the proposed total impurity limits will be evaluated/determined during the assessment of the application according to the applicable guidance.
[12] ICH Q3A(R2) and Q3B(R2) do not apply to certain NDA and ANDA products (i.e., products that are not "new drug products produced from chemically synthesised new drug substances" — biological/ biotechnological products, peptides, oligonucleotides, radiopharmaceuticals, fermentation products, and semi-synthetic products derived therefrom, herbal products, and crude products of animal or plant origin). However, the principles of these guidances and the principles of this MAPP may apply to drug substances and drug products (including some semi-synthetic and fermentation products, and peptides) submitted in NDAs and ANDAs.
[13] Ibid.

applicants should refer to relevant guidances[14,15,16] for determining AI limits for nitrosamines.

5. For some products, such as certain biotechnology and complex products, there may be impurities for which the relationship to stability, potency, or potential adverse clinical effects is not clear. This may be because the analytical techniques available have not allowed thorough characterization of the impurity, or data regarding the impact of the impurity on clinical performance are lacking, or the way that these products are manufactured does not allow for isolation and evaluation of impurities. For instance:

    - There may be a high level of uncertainty regarding the clinical impact of an impurity, such as a peptide- or protein-related impurity.

    - An impurity could be a surrogate for other impurities that might be clinically relevant or for which there is increased uncertainty. For example, for toxin-conjugated drug products, a surrogate may be free protein, fragmented protein, or free toxin, and used to represent the appearance or clearance of other dissociated parts of the toxin-conjugated product.

    In these scenarios, the control strategy, including impurity acceptance criteria, should include a risk-based evaluation considering both potential clinical impact and manufacturing process capability.

6. While establishment of impurity acceptance criteria should be guided by the totality of the data and consideration of the clinical impact of impurity levels instead of based solely on the manufacturing process capability, the pharmaceutical quality system should nonetheless monitor the drug substance and the drug product manufacturing process for their consistency and conformance to CGMP requirements.

7. Some impurities may increase the risk of unwanted immunogenicity. Immunogenicity risk assessments[17] for biologic products will use the existing assessment process and the principles outlined in the FDA guidance for industry *Immunogenicity Assessment for Therapeutic Protein Products* (August 2014*)*. Immunogenicity assay assessments for biologic products will use the existing assessment process and the principles

[14] See the guidance for industry *Control of Nitrosamine Impurities in Human Drugs* (September 2024) and the guidance for industry *Recommended Acceptable Intake Limits for Nitrosamine Drug Substance-Related Impurities* (August 2023).
[15] See the guidance for industry *Recommended Acceptable Intake Limits for Nitrosamine Drug Substance-Related Impurities* (August 2023).
[16] See the FDA guidance web page CDER Nitrosamine Impurity Acceptable Intake Limits, available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/cder-nitrosamine-impurity-acceptable-intake-limits, for more information.
[17] In this MAPP, the term *review* also means *assessment*, which is the term that CDER's Office of Pharmaceutical Quality and Office of Generic Drugs will generally use in place of *review*. *Assessment* means the process of both evaluating and analyzing submitted data and information to determine whether the application meets the requirements for approval and documenting that determination.

outlined in the FDA guidance for industry *Immunogenicity Testing of Therapeutic Protein Products – Developing and Validating Assays for Anti-Drug Antibody Detection* (January 2019) and other applicable guidances.

8. Impurity acceptance criteria should be informed by data derived from clinical trials, nonclinical studies (e.g., in silico modeling, in vitro, and animal studies), context of use, prior knowledge, publicly available information, and analytical capability, as appropriate. Product quality assessors should perform due diligence in evaluating impurities and the applicability of ICH Q3A(R2) or Q3B(R2) qualification threshold. The acceptability of impurity acceptance criteria is based on an assessment of the applicant's submitted safety rationale. The assessor's assessment may be informed by previous FDA experience (e.g., whether the potential risk of the impurity at the proposed acceptance criterion was addressed in an approved product), or information identified from the published literature.

9. Other review disciplines (e.g., pharmacology/toxicology (pharm/tox) and clinical) will use existing review processes for implementing this MAPP.

RESPONSIBILITIES

Responsibilities of the assessment teams in OPQ:

- Product quality assessors will discuss or consult with pharm/tox and/or computational toxicology, clinical, and clinical pharmacology review disciplines, as appropriate, when assessing the potential risk of a given impurity or impurities. Assessments or consults should be initiated as early as possible to allow sufficient time for adequate review. Product quality assessors should identify relevant information in an application before requesting a consult.

- Drug product quality assessors will evaluate the critical quality attributes (CQAs) associated with the drug substance, including the impurity acceptance criteria, to ensure that the drug product CQAs are appropriately identified and adequately controlled based on the consideration of clinical relevance and the desired product quality.

PROCEDURES

1. NDAs and ANDAs: Acceptance Criterion *Not More Than* the Qualification Threshold

1.1. For a specified impurity with a proposed acceptance criterion not more than the qualification threshold, absent other information to support the need for a lower limit, a proposed acceptance criterion up to the ICH Q3A(R2) or Q3B(R2) qualification threshold is generally acceptable.

1.2. Establishing impurities acceptance criteria at the ICH Q3A(R2) and Q3B(R2) qualification thresholds may not apply if any the following are true:

1.2.1 There are known safety data for the impurities based on their structural class (e.g., impurities known to be DNA reactive (i.e., mutagenic) or the presence of a structural alert for mutagenicity).

1.2.2 There is information suggesting that impurities of this class have unusually potent toxicities.

1.2.3 There are compendial acceptance criteria related to safety which are lower than the ICH qualification thresholds for the impurities.

1.2.4 There are immunological or other clinical concerns (e.g., pharmacokinetics/pharmacodynamics (PK/PD) activity, target population).

1.3 If the above information in section 1.2 suggests a concern with the proposed impurity acceptance criteria, then assessments or consults should be initiated early during the review cycle to allow sufficient time for adequate review:

1.3.1 For toxicology related concerns, the product quality assessor should request a pharm/tox evaluation to assess the risk to patients for impurities at a specified level. The product quality assessor should inform the pharm/tox reviewer or request a consult as early as possible (i.e., no later than mid-cycle review) in order for pharm/tox reviewer to request a risk assessment from the applicant, if necessary, for the proposed impurity acceptance criteria to facilitate a timely and specific review.

1.3.2 For immunological or other clinical concerns, the appropriate immunogenicity, clinical, and clinical pharmacology reviewers should be involved to assess the risk/benefit to patients. A consult should be issued if they are not already part of the assigned review team.

2. NDAs and ANDAs: Acceptance Criterion *Greater Than* the Qualification Threshold

2.1 For a specified impurity with a proposed acceptance criterion greater than the qualification threshold, the adequacy of the proposed acceptance criterion

should be assessed (see policy section, item 8). Assessments or consults should be initiated early during the review cycle to allow sufficient time for adequate review. In general, the product quality assessor should consult with the appropriate pharm/tox, clinical, and/or clinical pharmacology reviewers to conduct the following assessments in support of the proposed impurity acceptance criterion:

2.1.1 A pharm/tox assessment or consult for toxicology-related concerns (i.e., mutagenicity and/or general toxicity) to verify that impurities have been adequately evaluated and the levels of impurities are considered qualified in nonclinical studies and/or clinical trials.

2.1.2 Immunogenicity, clinical, and clinical pharmacology assessments or consults, as appropriate, for immunological or other clinical concerns to assess the risk in the context of the benefit of the product to patients.

2.2 In addition, the following should be considered in the assessment:

2.2.1 The proposed acceptance criterion may be supported by data demonstrating that the impurity is a metabolite.[18] Whether an impurity is considered qualified as a metabolite should be the subject of pharm/tox and/or clinical pharmacology assessments or consults.

2.2.2 The proposed acceptance criterion for an ANDA or a 505(b)(2) NDA product may be supported by a side-by-side comparative impurity analysis for the proposed product and the listed drug or RLD using the same analytical method that is shown to be suitable for its intended purpose. The comparative analysis is preferably to be conducted on multiple batches of the proposed product and the RLD. To support proposed new impurity or higher impurity acceptance criteria than that of the RLD, the applicant should submit a justification including a risk assessment (see section 2.1 above and section 3.2 below on risk assessment).

2.2.3 For products that (a) have USP monographs[19] or (b) do not have USP monographs but have other compendial monographs[20] and the monograph acceptance criteria are greater than the ICH Q3A(R2) or Q3B(R2) qualification thresholds, generally the impurity acceptance

[18] See the guidance for industry *Good ANDA Submission Practices Guidance for Industry* (January 2022).
[19] USP monographs are generally based on FDA-approved products. In cases where a discrepancy is noted between an FDA-approved product and the USP monograph, product quality assessors should inform the Compendial Operations and Standards Staff in the Office of Policy for Pharmaceutical Quality so that FDA can work with USP to revise the monograph.
[20] Refer to MAPP 5310.7 *Acceptability of Standards from Alternative Compendia (BP/EP/JP) for CDER policies on British Pharmacopoeia (BP)/European Pharmacopoeia (EP)/Japanese Pharmacopoeia (JP)* (September 2024).

criteria in those monographs may be considered acceptable based upon (1) nonclinical and clinical input for NDAs or (2) appropriate approved products (e.g., the RLD, other approved applications for the same drug) with the same maximum daily dose (MDD).[21]

2.2.4 If a potential risk has been identified, the proposed impurity acceptance criterion should be justified by the applicant. The applicant's justification should be evaluated by the product quality assessor (see Policy section, item 8) and if necessary, should request an assessment or a consult from a pharm/tox or clinical discipline for a safety evaluation.

2.2.5 For drug substances submitted in Drug Master Files in association with ANDAs, the impurity acceptance criteria for known specified impurities in USP monographs or other compendial monographs are generally considered to be acceptable for the DMF. The determination of the acceptability of the drug substance impurity acceptance criteria for the referencing application will be made by the drug product assessors (see Responsibility section).

3. BLAs and NDAs/ANDAs Excluded From ICH Q3A(R2) and Q3B(R2)

3.1. For those chemical drug substances and drug products (a) where there are compendial monographs or (b) that are NDA and ANDA products excluded from ICH Q3A(R2) and Q3B(R2) (e.g., peptides and some fermentation products), the recommendations outlined in sections 2.1 and 2.2 should be followed.

3.2. For all other products, such as biologics, a determination of the acceptability of the proposed acceptance criteria of impurities supported by a risk assessment should be made by the product quality assessor in consultation with other review disciplines including clinical, pharm/tox, immunogenicity, and clinical pharmacology, as appropriate. Assessments or consults should be initiated early during the review cycle to allow sufficient time for adequate review.

3.2.1 A risk assessment will generally consider the impact of an impurity on activity, PK/PD, safety, and immunogenicity.

3.2.2 A risk assessment can include clinical data, nonclinical data (e.g., in vitro data and animal data), prior knowledge, and publicly available information.

[21] If the product labeling is not clear, the product quality assessor should consult relevant disciplines within OGD or OND to obtain MDD information.

3.2.3 In some cases, uncertainty should be factored into the risk assessment. Uncertainty can be associated with the strength of the data to understand the clinical effect of an impurity as well as analytical capability and analytics performance to identify and characterize the impurity. Principles laid out in ICH Q9(R1)[22] and in an FDA scientific publication[23] describing how to manage the uncertainty with respect to the impact of product quality attributes on safety and/or efficacy may be followed.

3.2.4 Evaluation of immunogenicity risk assessment for impurities should be performed using a multidisciplinary approach, involving clinical, clinical pharmacology, pharm/tox, and/or product quality assessors.

3.2.5 For toxicology-related concerns, a pharm/tox assessment or consult should be made to verify that impurities have been adequately evaluated in nonclinical studies and/or clinical trials to assess the risk to patients for impurities at a specified level.

3.2.6 For the chemical drug component of a biologic-drug combination product (e.g., antibody-drug conjugate), the recommendations outlined in sections 1 and 2 should be followed.

3.2.7 For BLA products with or without USP monographs, the impurity acceptance criteria that are set according to principles outlined in the ICH guidance for industry *Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products* (August 1999) should generally be acceptable.

REFERENCES

Literature

- Rosenberg AS, Verthelyi D, and Cherney B, 2012, Managing Uncertainty: A Perspective on Risk Pertaining to Product Quality Attributes as They Bear on Immunogenicity of Therapeutic Proteins, J Pharm Sci (3560-7).

Guidances for Industry

[22] See the ICH guidance for industry *Q9(R1) Quality Risk Management* (May 2023).
[23] Managing Uncertainty: A Perspective on Risk Pertaining to Product Quality Attributes as They Bear on Immunogenicity of Therapeutic Proteins, J Pharm Sci, 2012 (3560-7).

- Draft guidance for industry *Establishing Impurity Specifications for Antibiotics* (April 2026).

- FDA-ICH guidance for industry *M7 Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk* (July 2023).

- FDA-ICH guidance for industry *M7 Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk – Question & Answers* (July 2023).

- FDA-ICH guidance for industry *Q3A Impurities in New Drug Substances* (Rev. 2, June 2008).

- FDA-ICH guidance for industry *Q3B Impurities in New Drug Products* (Rev. 2, August 2006).

- FDA-ICH guidance for industry *Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances* (December 2000).

- FDA-ICH guidance for industry *Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products* (August 1999).

- FDA-ICH guidance for industry *Q9(R1) Quality Risk Management* (May 2023).

- Guidance for industry *ANDAs: Impurities in Drug Substances* (July 2009).

- Guidance for industry *ANDAs: Impurities in Drug Products* (November 2010).

- Guidance for industry *Control of Nitrosamine Impurities in Human Drugs* (September 2024).

- Guidance for industry *Good ANDA Submission Practices Guidance for Industry* (January 2022).

- Guidance for industry *Immunogenicity Assessment for Therapeutic Protein Products* (August 2014).

- Guidance for industry *Immunogenicity Testing of Therapeutic Protein Products – Developing and Validating Assays for Anti-Drug Antibody Detection* (January 2019).

- Guidance for industry *Recommended Acceptable Intake Limits for Nitrosamine Drug Substance-Related Impurities* (August 2023).

MAPP

- MAPP 5310.7 *Acceptability of Standards from Alternative Compendia (BP/EP/JP) for CDER policies on British Pharmacopoeia (BP)/European Pharmacopoeia (EP)/Japanese Pharmacopoeia (JP)* (September 2024).

FDA Web Page

- FDA guidance web page CDER Nitrosamine Impurity Acceptable Intake Limits, available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/cder-nitrosamine-impurity-acceptable-intake-limits.

DEFINITIONS

- Contaminant: Any adventitiously introduced materials not intended to be part of the manufacturing process.

- Impurity (chemical substances): (1) Any component of the new drug substance which is not the chemical entity defined as the new drug substance. (2) Any component of the drug product which is not the chemical entity defined as the drug substance or an excipient in the drug product (ICH Q6A *Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances* (December 2000)).

- Impurity (biotechnology/biological products): Any component present in the drug substance or drug product which is not the desired product, a product-related substance, or excipient including buffer components. It may be either process- or product-related (ICH Q6B *Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products* (August 1999)).

- Specification: Defined in ICH Q6A and Q6B as a list of tests, references to analytical procedures, and appropriate acceptance criteria which are numerical limits, ranges, or other criteria for the tests described. It establishes the set of criteria to which a drug substance, drug product or materials at other stages of its manufacture should conform to be considered acceptable for its intended use. “Conformance to specifications” means that the drug substance and/or drug product, when tested according to the listed analytical procedures, will meet the listed acceptance criteria. Specifications are critical quality standards

that are proposed and justified by the manufacturer and approved by regulatory authorities as conditions of approval.

EFFECTIVE DATE

- This MAPP is effective on 05/13/26.

CHANGE CONTROL TABLE

Effective Date	Revision Number	Revisions
1/18/18	Initial	N/A
9/19/18	Rev. 1	Revised subsection 2.2.3 under PROCEDURES for further clarity.
5/1/2020	N/A	Administrative: organizational name change from Compendial Operations and Standards Branch to Compendial Operations and Standards Staff, changes to definition of protein to reflect section 351(i) of the PHS Act as amended by the Further Consolidated Appropriations Act of 2020.
05/13/26	Rev. 2	Include unspecified impurities in establishing the acceptance criteria for total impurity; include a statement that a monograph limit should only be allowed if it complies with the impurity limits based on the MDD of the approved drug product; clarify responsibilities for drug product assessors; update references to include nitrosamine guidances.