POLICY AND PROCEDURES

Office of Pharmaceutical Quality

Establishing 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 establishing 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 ICH Q3A(R2) and Q3B(R2)[3] apply to new molecular entities produced by chemical synthesis, 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, and synthetic peptides,[4] submitted in NDAs and ANDAs.

The principles in this MAPP may also be used to establish acceptance criteria for DNA-reactive (i.e., mutagenic) impurities that are generally controlled at tighter limits according to the ICH M7.[5]

[1] In this MAPP, *impurity* can refer to 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 5 and 6 in the References section.
[4] ICH Q3A(R2) and Q3B(R2) do not apply to certain NDA and ANDA products (e.g., peptides, oligonucleotides, fermentation products, and semi-synthetic products).
[5] See 7 in References section.

The principles in this MAPP may also apply to investigational drug substances and drug products, depending on the risk.

Where the active ingredient is a single enantiomer, the principles in this MAPP may also apply to associated enantiomeric impurities.

Please note that 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 needs to be established on a case-by-case basis.

The following are excluded from this MAPP:

- Residual solvents and elemental impurities, as these are adequately addressed in ICH Q3C and ICH Q3D. Refer to ICH Q3C and ICH Q3D for establishing limits for these impurities.

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

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

- Leachables from the container closure system.[6]

- Polymorphic forms[7]

BACKGROUND

To provide assurance that a product performs as is intended, there is a need to establish impurity acceptance criteria. 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 (listed drug or reference listed drug (RLD)), analytical precision of the method used to measure the impurity, and manufacturing process capability. The intent of this MAPP is to clarify the types of data and information needed as well as the limitations when establishing impurity acceptance criteria. In general, the types of data and information should be guided by the

[6] Refer to ICH Q6A for a discussion on establishing a specification for extractables for oral solutions.
[7] Refer to ICH Q6A for a discussion on the need to set acceptance criteria for polymorphic forms.

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 Q6A should generally be applied to NDA and ANDA products. Specifically, a specification should include the following, where "specified impurity" is any impurity present at greater than the identification threshold:

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

[8] ICH M3(R2) defines that significant human metabolite(s) are those that occur at exposures greater than 10 percent of total drug-related exposure.

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 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)[9]
   (c) Products submitted in BLAs[9]

   For impurities listed in a specification, the 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,[10] and analytical capability, as appropriate.

4. 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 either because the analytical techniques available have not allowed thorough characterization of the impurity, or because data regarding the impact of the impurity on clinical performance are lacking. 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 greater consideration for manufacturing process capability.

5. 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 basing the impurity limits solely on the manufacturing process capability, the

[9] ICH Q3A(R2) and Q3B(R2) do not apply to BLAs and 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 synthetic peptides) submitted in NDAs and ANDAs.

[10] Publicly available information includes but is not limited to: scientific literature, FDA approved package insert, and FDA research and assessment.

manufacturing process consistency should be monitored during the production of the drug substance and the drug product as part of the quality system.

6. Office of Biotechnology Products (OBP) immunogenicity reviewers will use the existing review process and the principles outlined in the FDA guidance for industry *Immunogenicity Assessment for Therapeutic Protein Products* to assess the immunogenicity risk of a given impurity for implementing this MAPP.

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

RESPONSIBILITIES

Responsibilities of the review teams in OPQ:

- Product quality reviewers 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 reviewers should identify relevant information in an application before requesting a consult.

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. Product quality reviewers should perform due diligence in evaluating impurities and the applicability of ICH threshold levels. This evaluation may be based on a review of the applicant's submitted safety rationale, previous FDA experience with identical impurities within CDER-regulated products considering the context of use, or information identified from the published literature. 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 limits related to safety which are lower than the ICH qualification thresholds for the impurities.[11]

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

1.3 If the above information suggests a concern with the proposed impurity level, 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 reviewer should request a pharm/tox evaluation to assess the risk to patients for impurities at a specified level.

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, data from clinical trials, nonclinical (i.e., in silico, in vitro, and animal) studies, prior knowledge, and publicly available information, including those on significant human metabolites provided by the applicant, should be used by the review disciplines, as appropriate, to assess the adequacy of the proposed acceptance criterion. Assessments or consults should be initiated early during the review cycle to allow sufficient time for adequate review. In general, the product quality reviewer should consult with the appropriate pharm/tox, clinical, and/or clinical pharmacology reviewers to conduct the following assessments in support of the proposed impurity level:

2.1.1 A pharm/tox assessment or consult for toxicology-related concerns to verify that impurities have been adequately evaluated and the levels of

[11] When a compendial limit for an impurity is below the qualification threshold, reviewers should perform due diligence to ensure that this limit is derived from an FDA-approved product and justified based upon an identified safety issue rather than on process capability. In cases where a discrepancy is noted between an FDA-approved product and the USP monograph, product quality reviewers should inform the Compendial Operations and Standards Branch in the Office of Policy for Pharmaceutical Quality so that FDA can work with USP to revise the monograph.

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/benefit 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 the data demonstrating that the impurity is a significant metabolite. Whether a metabolite is clinically significant should be the subject of pharm/tox and/or clinical pharmacology 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 impurities or higher impurity levels than that of the RLD, the applicant should submit a justification including a risk assessment (see section 3.2 below on risk assessment).

2.2.3 For those products that have USP monographs[12] or other compendial monographs[13] and the monograph acceptance criteria are greater than the ICH Q3A(R2) or Q3B(R2) qualification thresholds, the monograph limits may be used only if the limit is justified in an FDA-approved product.

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 monographs apply or (b) that are ANDA and 505(b)(2) NDA products (e.g., peptides and fermentation products) and are not transitioning to BLA under the Biologics Price Competition and Innovation Act of 2009, recommendations outlined in the above 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

[12] 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 reviewers should inform the Compendial Operations and Standards Branch in the Office of Policy for Pharmaceutical Quality so that FDA can work with USP to revise the monograph.

[13] 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).

should be made by the product quality reviewer 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.

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 the ICH Q9[14] and in an FDA scientific publication[15] 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 For immunological concerns regarding products not reviewed by OBP, an immunogenicity consult may be requested from OBP to assess the immunogenicity risk of the impurities. The clinical reviewer on the review team will also evaluate the risk to patients.

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.

REFERENCES

1. FDA guidance for industry *ANDAs: Impurities in Drug Substances* (2009).

2. FDA guidance for industry *ANDAs: Impurities in Drug Products* (2010).

3. FDA guidance for industry *Biosimilars: Additional Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009* (Revision 1, 2015).

[14] See 10 in References section.
[15] 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).

4. FDA guidance for industry *Immunogenicity Assessment for Therapeutic Protein Products* (2014).

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

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

7. FDA-ICH guidance for industry *M7 Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk* (2015).

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

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

10. FDA-ICH guidance for industry *Q9 Quality Risk Management* (2006).

11. 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).

DEFINITIONS

- **Biological product**: Defined in section 351(i)(1) of the Public Health Service (PHS) Act as a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein (except any chemically synthesized polypeptide), or analogous product, or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of a disease or condition of human beings. A chemically synthesized polypeptide means any alpha amino acid polymer that (a) is made entirely by chemical synthesis, and (b) is less than 100 amino acids in size.[16]

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

[16] See FDA guidance for industry *Biosimilars: Additional Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009.* We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance web page at https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

- **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 for "Chemical Substances")

- **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 for "Biotechnological/Biological Products")

- **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 January 18, 2018.

CHANGE CONTROL TABLE

Effective Date	Revision Number	Revisions
1/18/18	Initial	N/A