OFFICE OF NEW ANIMAL DRUG EVALUATION REVIEWER'S CHAPTER

ESTABLISHING IMPURITY ACCEPTANCE CRITERIA NOT EXCEEDING CENTER FOR VETERINARY MEDICINE GUIDANCE FOR INDUSTRY (GFI) #92 AND GFI #93 RECOMMENDED QUALIFICATION THRESHOLDS FOR NEW AND ABBREVIATED ANIMAL DRUG APPLICATIONS

I. PURPOSE

This document provides guiding principles for ONADE reviewers of Chemistry, Manufacturing, and Controls (CMC) information relating to establishing drug substance and drug product impurity acceptance criteria for impurities in (abbreviated) new animal drug applications [(A)NADAs], when such acceptance criteria do not exceed the recommended qualification thresholds defined in CVM Guidances for Industry (GFIs). Specifically, the CVM GFIs that contain the information on thresholds are GFI #92 "Impurities In New Veterinary Drug Substances (Revision)" [Veterinary International Conference on Harmonization (VICH) Technical Requirements for Registration of Veterinary Medicinal Products GL10(R)] and GFI #93 "Impurities In New Veterinary Medicinal Products (Revision)" [VICH GL11(R)]. The intent of this document is to clarify the types of data and information the CMC reviewer may consider when assessing impurity acceptance criteria that do not exceed CVM GFI #92 and CVM GFI #93 qualification thresholds. The principles in this document may also apply to review of:

- Type II drug master files (DMF) and veterinary master files (VMF) (see P&P 1243.2400); and
- (generic) investigational new animal drug [(J)INAD] files.

CVM GFI #92 [VICH GL10(R)] and CVM GFI #93 [VICH GL11(R)], hereafter referred to by their GFI numbers, apply to new veterinary drug substances and new veterinary medicinal products produced by chemical synthesis. But the principles that inform those guidance documents and the principles of this P&P may be considered in the review of other drug substances and drug products, including some semi-synthetic and non-complex, well-characterized fermentation products (see CVM GFI #216 "Fermentation-Derived Intermediates, Drug Substances, and Related Drug Products for Veterinary Medicinal Use"), and synthetic peptides, submitted in (A)NADAs.

The following are excluded from this document:

- impurities known to produce toxic or significant pharmacological effects;
- impurities with proposed acceptance criteria exceeding the relevant CVM GFIs #92 or #93 recommended qualification threshold;

- residual solvents and elemental impurities. As these are addressed in CVM GFI #100 “Impurities: Residual Solvents in New Veterinary Medicinal Products, Active Substances and Excipients (Revision)” [VICH GL18(R)] and CVM GFI #255 “Elemental Impurities in Animal Drug Products Questions and Answers”;
- extraneous contaminants that should not occur in new animal drug substances and drug products and are appropriately addressed by Good Manufacturing Practices;
- microbiological attributes (e.g., endotoxin, microbial limits);
- leachables from the container closure system and process leachables;
- enantiomeric impurities; and
- polymorphic forms.

Definitions of terms used in this document are defined in the glossary sections of the relevant cited guidance documents, CVM GFIs #92 and #93.

Note that as guidance, CVM GFIs #92 and #93 do not create binding requirements, but represent CVM’s current thinking and describe actions consistent with legal and regulatory requirements as currently interpreted by FDA. Therefore, it is appropriate for reviewers of CMC information to refer to those GFIs when completing their work.

II. BACKGROUND

Impurity acceptance criteria are reviewed as part of a drug substance or drug product specification to assure that a product performs as intended. In general, we recognize that the recommended thresholds established in these VICH guidance documents may serve as acceptable limits for the establishment of acceptance criteria for impurities in drug applications. When available, clinical data are also relevant.

Table 1: GFI #92 Recommended Thresholds for New Animal Drug Substances

Identification[2]	As per ICH Q3A(R2)[*] 0.20%[**]
Reporting[1,2]	As per ICH Q3A(R2)[*] 0.10%[**]
Qualification[2]	0.50%

* New veterinary drug substance used in veterinary and human medicine
** New veterinary drug substance not used in human medicine
1 Higher reporting thresholds should be scientifically justified.
2 Lower thresholds may be appropriate if the impurity is unusually potent or has toxicity, immunological, pharmacological, or clinical concerns.

Table 2: GFI #93 Recommended Thresholds for New Veterinary Medicinal Products

Identification[1,2]	1.0%
Reporting[1,2]	0.3%
Qualification[1,2]	1.0%

1 Higher thresholds should be scientifically justified.
2 Lower thresholds may be appropriate if the impurity is unusually potent or has toxicity, immunological, pharmacological, or clinical concerns.

III. POLICY

1. Including the following list of impurities described in CVM GFIs #92 and #93 in new veterinary drug substances and new veterinary medicinal products specifications is appropriate. This includes the accurate usage of common terms employed in the listing of impurities, such as "degradant," "process impurity," and "related substance."

   Drug Substance

   - Each specified identified impurity
   - Each specified unidentified impurity (e.g., "Impurity A" or "RRT 1.43")
   - 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 (e.g., "Degradant A" or "RRT 1.43")
   - Any unspecified degradation product, with an acceptance criterion of not more than the identification threshold
   - Total degradation products

2. Establishing acceptance criteria for impurities in drug substances

   a. A limit of 0.50% (the CVM GFI #92 recommended qualification threshold) will generally be acceptable for identified impurities. A limit of 0.20% (the CVM GFI #92 recommended identification threshold) will generally be acceptable for unidentified impurities. For impurities known to be unusually potent, or have toxicity immunological, pharmacological, or clinical concerns, the proposed acceptance criteria based solely on qualification thresholds listed in CVM GFI #92 are not sufficient and need to be adequately justified. The establishment of acceptance criteria for such impurities are outside the scope of this document.

   b. The acceptance criterion for total impurities in drug substances should consider an acceptable specification for individual impurities and degradants determined in the evaluation of available stability data. It will be useful to evaluate the firm's proposed acceptance criterion for adherence to at least one of the below justifications.

      i. Generally, the criterion for total impurities should not exceed the summation of acceptance criteria for individual specified (identified and unidentified) impurities and degradants.

ii. Alternatively, the acceptance criterion for total impurities in drug substances can be based on the summation of observed impurities and degradants, at a level greater than the CVM GFI #92 recommended reporting threshold (0.10%), allowing sufficient latitude for normal analytical and manufacturing variation.

The total impurity acceptance criterion should not exceed thresholds that may compromise the potency/assay through expiry.

3. Establishing acceptance criteria for degradants in drug products

   a. Per CVM GFI #93: "Generally, impurities present in the new veterinary drug substance need not be monitored or specified in the new veterinary medicinal product unless they are also degradation products."

   b. A limit of 1.0% (the CVM GFI #93 recommended qualification threshold) will generally be acceptable for specified degradants (identified or unidentified). For impurities known to be unusually potent, toxic, or have immunological, pharmacological, or clinical concerns, the proposed acceptance criteria based solely on CVM GFI #93 qualification thresholds are not sufficient and need to be justified. The establishment of acceptance criteria for such impurities are outside the scope of this document.

   c. The acceptance criterion for total degradants in drug products should be based on an acceptable specification for individual degradants and degradants determined in the evaluation of available stability data. The sponsor's proposed acceptance criterion should be evaluated for adherence to at least one of the below justifications.

      i. Generally, the criterion for total degradants in drug products should not exceed the summation of acceptance criteria for individual specified (identified and unidentified) degradants.

      ii. Alternatively, the acceptance criterion for total degradants in drug products can be based on the summation of observed degradants at a level greater than the CVM GFI #93 (VICH GL11(R)) recommended reporting threshold, allowing sufficient latitude for normal analytical and manufacturing variation.

      The total degradation acceptance criterion should not exceed thresholds that may compromise product potency/assay through product expiry.

4. While establishment of impurity acceptance criteria may be guided by adoption of VICH thresholds, firms should still demonstrate sufficient control of their manufacturing process and evaluate consistency during the production of the drug substance and the drug product as part of the quality system.

IV. RESPONSIBILITIES

CMC reviewers will consider the recommended thresholds described in CVM GFIs #92 and #93 to evaluate the proposed acceptance criteria. In cases where there is concern that a given impurity may be unusually potent, toxic, or have immunological, pharmacological, or clinical concerns, the reviewer may need to discuss or consult with the appropriate review division(s) or the toxicology team in the Division of Human Food

Safety. Determination that an impurity may fall into one of these categories is generally not the responsibility of the CMC reviewer. Such a determination is the responsibility of the sponsor as part of pharmaceutical development and/or clinical studies and noted when establishing these limits. The establishment of acceptance criteria for such impurities are outside the scope of this document.

V. PROCEDURES

To assess the acceptability of proposed impurity specifications, the following are relevant considerations for CMC reviewers:

1. Regarding the listing of impurities in the proposed specification, inclusion of the list of impurities and degradation products per CVM GFIs #92 and #93 (see Section III.1) in the proposed specification, including unspecified and total impurities/degradants, is appropriate. The reviewer may also consider the following when determining the acceptability of the proposed specifications:

    a. The inclusion of impurities/degradants in the proposed specification should be based on the impurities/degradants found in batches manufactured by the proposed commercial process and observed under recommended storage conditions.

    b. Of note, significant distinctions exist in the establishment of impurity specifications for drug substances and drug products.

        i. Drug Substance: Acceptable impurity specifications for drug substances should control degradation products *in addition to* process impurities. Refer to CVM GFI #92, Sections 2 and 3, for a description of categories of impurities which are controlled at the level of the drug substance.

        ii. Drug Product: CVM GFI #93 addresses only those impurities in new veterinary medicinal products classified as degradation products. Therefore, acceptable degradant specifications in drug products will ensure that all degradation products are controlled. A sponsor may also include specifications for process impurities that are controlled at the level of the drug substance. However, if the process impurities are not also degradants, then reviewers should ensure that they are not included in the calculation of the total degradant acceptance criterion. Refer to CVM GFI #93, Section V, for a description of additional considerations for the inclusion of degradants in the drug product specification.

2. For the individual impurities/degradants listed in the specification as per the considerations in point 1, reviewers should then assess the acceptability of the proposed acceptance criteria per Section III.2 and III.3.

3. The reviewer should determine whether the acceptance criterion for total impurities has been established based on the considerations outlined in Section III.3.

4. Establishing impurities acceptance criteria at the CVM GFIs #92 and #93 recommended qualification thresholds may not apply if the following are true:

    a. Data are present from pivotal safety studies that indicate that a tighter limit may be necessary [e.g., pharmacokinetics/pharmacodynamics (PK/PD) activity, adverse events in target animal species].

b. The impurity is known to produce toxic or significant pharmacological effects. As applicable, this information should be included by the API manufacturer in the corresponding master file or submitted by the drug product sponsor to the (A)NADA.

c. There are United States Pharmacopeia (USP) compendial limits which are lower than the qualification thresholds for the impurities. In cases where the established USP limit may not be appropriate for veterinary products, the sponsor may provide a justification for CVM review. This may be a situation in which the reviewer would refer sponsors to the July 10, 2019 draft GFI entitled Harmonizing Compendial Standards With Drug Application Approval Using the USP Pending Monograph Process.

5. If the above information suggests a concern with the proposed impurity level, CMC reviewers should consult their team leaders and the Impurities Working Group. Assessments or consults[1] should be initiated early in the review cycle to allow sufficient time for adequate review.

VI. REFERENCES

CVM Guidance for Industry

92 - Impurities in New Veterinary Drug Substances (Revision) VICH GL10(R)

93 - Impurities in New Veterinary Drug Products (Revision) VICH GL11(R)

100 – Residual Solvents in New Veterinary Medical Products VICH GL18

216 – Chemistry, Manufacturing, and Controls (CMC) Information — Fermentation-Derived Intermediates, Drug Substances, and Related Drug Products for Veterinary Medicinal Use

255 – Elemental Impurities in Animal Drug Products Questions and Answers

Center for Drug Evaluation and Research (CDER) Manual of Policies & Procedures

MAPP 5017.2 Rev. 1 - Establishing Impurity Acceptance Criteria As Part of Specifications for NDAs, ANDAs, and BLAs Based on Clinical Relevance

Center for Drug Evaluation and Research and Center for Biologics Evaluation and Research Guidance for Industry

Q3A(R) Impurities in New Drug Substances

Q3B(R) Impurities in New Drug Products (Revision 2)

CDER and CVM Guidance for Industry

Draft Guidance - Harmonizing Compendial Standards With Drug Application Approval Using the USP Pending Monograph Process

[1] See P&P 1243.3200

VII. VERSION HISTORY

January 25, 2021 – Original version.

July 14, 2021 – Edits were made to clarify that the recommendations in GFI #92 and #93 are not binding, in addition to minor editorial changes.

July 14, 2022 – Quality systems review for minor formatting updates.

May 25, 2023 - Quality system review conducted of the document and no updates or revisions were necessary at this time. To bring all office quality system documentation into compliance with the FDA Visual Identity Program approved fonts, ONADE has adopted Arial 11-point font. The font of this document was changed from Verdana 10-point font to Arial 11-point font.