NDA Impurities in New Drug Substances.

IAGIM Scientific Committee
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DRAFT **Q3A(R)** GUIDANCE FOR INDUSTRY

INTRODUCTION

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NEW DRAFT REVISED GUIDANCE ON IMPURITIES IN NEW DRUG SUBSTANCES

SUMMARY:

The Food and Drug Administration (FDA) published a DRAFT revised guidance entitled ‘‘**Q3A(R)** Impurities in New Drug Substances.’’ The **(R)** Implies a revised guidance previously issued.

The DRAFT revised guidance, which updates the guidance on the same topic published in the Federal Register of January 4, **1996** (**the 1996 guidance**),

The draft revised guidance is **not** intended to apply to new drug substances used during the clinical research stage of development or clinical trials.

The draft revised guidance also does **not** apply to:

- biological/biotechnological substances, peptides
- oligonucleotides
- radiopharmaceuticals
- fermentation and semisynthetic products derived from that process,
- herbal products, and
- crude products of animal or plant origin.

Impurities in new drug substances are addressed in the draft revised guidance from two different perspectives namely:

IDENTIFICATION & SAFETY

- CHEMISTRY ASPECTS

Classification and identification of impurities, report generation, setting specifications, and a brief discussion of analytical procedures; and

- SAFETY ASPECTS

Guidance for qualifying impurities that were not present in batches of the new drug substance used in safety and clinical studies and/or impurity levels substantially higher than in those batches.

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The draft revised guidance includes revised text on threshold limits, revised text on specification limits for impurities, and new guidance on rounding. Additions to the glossary include definitions for the terms ‘‘identification threshold,’’ ‘‘qualification threshold,’’ ‘‘reporting threshold,’’ and ‘‘rounding.’’ References to validated limit of quantitation were removed.

Guide proposes ROUNDING impurity assays up to 0.1%

The section on solvents references a more recently published ICH guidance entitled ‘‘Q3C Impurities: Residual Solvents.’’

Minor editorial changes were made to improve the clarity and consistency of the document.

The text of the draft revised guidance follows:

Q3A(R) Impurities in New Drug Substances (NDAs).

1. Preamble

This document is intended to provide guidance for registration applications on the content and qualification of impurities in new drug substances produced by chemical syntheses and not previously registered in a region or member State.

This Q3A(r) Guidance is only for NDAs

It is not intended to apply to the regulation of new drug substances used during the clinical research stage of development.

- Biological/ biotechnological
- peptide
- oligonucleotide
- radiopharmaceutical
- fermentation and
- semisynthetic products derived therefrom, herbal products, and
- crude products of animal or plant origin are not covered.

Impurities in new drug substances are addressed from two perspectives:

Chemistry aspects

Include classification and identification of impurities, report generation, setting specifications, and a brief discussion of analytical procedures; and

Safety aspects

Include specific guidance for qualifying impurities that were not present in batches of new drug substance used in safety and clinical studies and/or impurity levels substantially higher than in those batches.

Threshold limits are defined, at or below which qualification is not needed.

2.CLASSIFICATION of IMPURITIES

Impurities may be classified into the following three key categories:

- ORGANIC IMPURITIES (Process- and Drug-Related)
- INORGANIC IMPURITIES
- RESIDUAL SOLVENTS

ORGANIC IMPURITIES may arise during the manufacturing process and / or storage of the new drug substance.

They may be identified or unidentified, volatile or non-volatile, and include:

- Starting Materials
- By-Products
- Intermediates
- Degradation Products
- Reagents, Ligands, and Catalysts

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INORGANIC IMPURITIES may derive from the manufacturing process. They are normally known and identified, and include:

- Reagents, Ligands, and Catalysts
- Heavy Metals or Other Residual Metals
- Inorganic Salts

ORGANIC Degradants are the only Important Impurities

Solvents are organic or inorganic liquids used during the manufacturing process. Since these are generally of known toxicity, the selection of appropriate controls is easily accomplished (see ICH Q3C Impurities: Residual Solvents).

WHAT IS NOT ADDRESSED

Excluded from this document are: Extraneous contaminants (other materials such as filter aids, charcoal) that should not occur in new drug substances and are more appropriately addressed as good manufacturing practice (GMP) issues; polymorphic form, a solid state property of the new drug substance; and enantiomeric impurities.

3. Rationale for the Reporting and Control of Impurities

3.1 Organic Impurities

The applicant should summarize those actual and potential impurities most likely to arise during the synthesis, purification, and storage of the new drug substance.

This summary should be based on sound scientific appraisal of the chemical reactions involved in the synthesis, impurities associated with raw materials that could contribute to the impurity profile of the new drug substance, and possible degradation products.

TABULATE Impurities that Could & Do Arise

This discussion may include only those impurities that may reasonably be expected based on knowledge of the chemical reactions and conditions involved. In addition, the applicant should summarize the laboratory studies conducted to detect impurities in the new drug substance.

This summary should include test results of batches manufactured during the development process and batches from the proposed commercial process, as well as results of intentional degradation studies used to identify potential impurities arising during storage.

Assessment of the proposed commercial process may be deferred until the first batch is produced for marketing.

COMPARE Developmental & Commercial Lot Impurities

The impurity profile of the drug substance lots intended for marketing should be compared with those used in development, and any differences discussed.

The studies conducted to characterize the structure of actual impurities present

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in the new drug substance at a level greater than (>) the threshold given in Attachment 1 (e.g., calculated using the response factor of the drug substance) should be described.

Note that all specified impurities at a level greater than (>) the identification threshold in batches manufactured by the proposed commercial process should be identified.

Degradation products observed in stability studies at recommended storage conditions should be similarly identified.

When identification of an impurity is not feasible, a summary of the laboratory studies demonstrating the unsuccessful effort should be included in the application.

Where attempts have been made to identify impurities present at levels of not more than (<) the identification thresholds, it is useful to also report the results of these studies.

Identification of impurities present at an apparent level of not more than (<) the identification threshold is generally not necessary.

However, analytical procedures should be developed for those potential impurities that are expected to be unusually potent, producing toxic or pharmacologic effects at a level less than or equal to (<) the identification threshold.

All impurities should be qualified as described later in this guidance.

Conventional rounding rules should be applied, and the results presented with the same number of decimals as given in the limit (see glossary).

Agency's Rounding Example Violates Conventional Rules

3.2 Inorganic Impurities

Inorganic impurities are detected and quantitated using pharmacopoeial or other appropriate procedures.

Carryover of catalysts to the new drug substance should be evaluated during development. The need for inclusion or exclusion of inorganic impurities in the new drug substance specifications should be discussed. Limits should be based on pharmacopoeial standards or known safety data.

3.3 Solvents

The control of residues of the solvents used in the manufacturing process for the new drug substance should be discussed and presented according to the ICH Q3C guidance for residual solvents.

4. Analytical Procedures

The registration application should include documented evidence that the analytical procedures are validated and suitable for the detection and quantitation of impurities (see ICH Q2A and Q2B guidances for analytical validation - also new draft guidelines Sept 2000).

Differences in the analytical procedures used during development and those proposed for the commercial product should be discussed in the registration application.

Organic impurity levels can be measured by a variety of techniques, including those which compare an analytical response for an impurity to that of an appropriate reference standard or to the response of the new drug substance itself.

Reference standards used in the analytical procedures for control of impurities should be evaluated and characterized according to their intended uses.

It is considered acceptable to use the drug substance as a standard to estimate the levels of impurities.

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In cases where the response factors are not close, this practice may still be acceptable, provided a correction factor is applied or the impurities are, in fact, being overestimated.

Specifications and analytical procedures used to estimate identified or unidentified impurities are often based on analytical assumptions (e.g., equivalent detector response).

These assumptions should be discussed in the registration application.

5. Reporting Impurity Content of Batches

Analytical results should be provided for all batches of the new drug substance used for clinical, safety, and stability testing, as well as for batches representative of the proposed commercial process.

Batch Analysis
Comparative
Reporting Required

The content of individual identified and unidentified and total impurities observed in these batches of the new drug substance should be reported with the analytical procedures indicated.

A tabulation (e.g., spreadsheet) of the data is recommended. Impurities should be designated by code number or by an appropriate descriptor, e.g., retention time.

Levels of impurities that are not more than (>) the reporting threshold given in Attachment 1 need not be reported.

A higher reporting threshold should only be proposed with justification.

All impurities at a level greater than (>) the reporting threshold should be summed and reported as Total Impurities.

The summation should be performed on the unrounded individual values, and the total value should be rounded and reported as described in section 3.1.

JOURNAL EDITORIAL COMMENT

ROUNDING RESOLUTION NEEDED

The agency needs to resolve this dichotomy of rounding definitions and create a clear standard operation procedure for the reporting of impurity assays, irrespective of whether the test is for a branded or generic drug. Currently a clear and precise definition to "rounding procedures " needs to be understood by both agency and industry alike.

FUTURE ROUNDING IMPACT

The question arises does the analytical reporting procedures change according to the different agency rounding procedures as the product status shifts from a new drug product to a generic product, on patent expiration.

TWO ROUNDING DEFINITIONS

Section 3.1 Organic Impurities of the proposed guidance *(Q3AR)* states: Conventional rounding rules should be applied, and the results presented with the same number of decimals as given in the limit (see glossary … For example, a result greater than or equal to (≥) 0.05 and less than (<) 0.15 is rounded to 0.1.).

When analytical procedures change during development, reported results should be linked to the procedure used, with appropriate validation information provided.

Representative chromatograms should be provided.

Always Include
Clear
Chromatograms
in Reports/Profiles

Chromatograms of such representative batches from methods validation studies showing separation and detectability of impurities (e.g., on spiked samples), along with any other impurity tests routinely performed, can serve as the representative impurity profiles.

The applicant should ensure that complete impurity profiles

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(i.e., chromatograms) of individual batches are available if requested.

A tabulation should be provided that links the specific new drug substance batch to each safety study and each clinical study in which it has been used.

Reference each Development Lot to the Analytical Assay

For each batch of the new drug substance, the report should include:

Batch Identity and Size

Date of Manufacture

Site of Manufacture

Manufacturing Process

Impurity Content, Individual and Total

Use of Batches

Reference to Analytical Procedure Used

6. **Specifications for Impurities**

The specifications for a new drug substance should include limits for impurities. Stability studies, chemical development studies, and routine batch analyses can be used to predict those impurities likely to occur in the commercial product.

Specified Impurities are identified or unidentified

The selection of impurities to include in the new drug substance specifications should be based on the impurities found in batches manufactured by the proposed commercial process.

Those impurities selected for inclusion in the specifications for the new drug substance are referred to as ‘‘specified impurities’’ in this guidance.

Specified impurities may be identified or unidentified and should be individually listed in the new drug substance specifications.

A rationale for the inclusion or exclusion of impurities in the specifications should be presented.

This rationale should include a discussion of the impurity profiles observed in the safety and clinical development batches, together with a consideration of the impurity profile of material manufactured by the proposed commercial process.

Specific identified impurities should be included along with specified unidentified impurities estimated to be present at a level greater than (>) the qualification / identification threshold given in Attachment 1.

Side-by-side Comparisons of Development & Clinical with actual Commercial Lots

For impurities known to be unusually potent or to produce toxic or unexpected pharmacological effects, the quantitation/detection limit of the analytical methods should be commensurate with the level at which the impurities must be controlled.

For unidentified impurities, the procedure used and assumptions made in establishing the level of the impurity should be clearly stated.

Specified unidentified impurities included in the specifications should be referred to by an appropriate qualitative analytical descriptive label (e.g., ‘‘unidentified A,’’ ‘‘unidentified with relative retention of 0.9’’).

Finally, a general specification limit of not more than (<) the qualification/identification threshold (Attachment 1) for any unspecified impurity should be included.

Limits should be set no higher than the

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level that can be justified by safety data and consistent with the level achievable by the manufacturing process and the analytical capability.

Where there is no safety concern, impurity specifications should be based on data generated on batches of the new drug substance manufactured by the proposed commercial process, allowing sufficient latitude to deal with normal manufacturing and analytical variation, and the stability characteristics of the new drug substance.

Batch-To-Batch Variations Impact on Validation

Although normal manufacturing variations are expected, significant variation in batch-to-batch impurity levels may indicate that the manufacturing process of the new drug substance is not adequately controlled and validated (see ICH Q6A guidance on specifications).

In summary, the new drug substance specifications should include, where applicable, limits for:

Organic Impurities

Each Specified Identified Impurity

Each Specified Unidentified Impurity at a level greater than (>) the qualification/ identification threshold

Any Unspecified Impurity with a limit of not more than (<) the qualification/ identification threshold Total Impurities

Residual Solvents

Inorganic Impurities

Keep Unspecified Impurities BELOW 0.05

7. QUALIFICATION OF IMPURITIES

Qualification is the process of acquiring and evaluating data that establishes the biological safety of an individual impurity or a given impurity profile at the level(s) specified.

The applicant should provide a rationale for selecting impurity limits based on safety considerations.

The level of any impurity present in a new drug substance that has been adequately tested in safety and/ or clinical studies is considered qualified. Impurities that are also significant metabolites present in animal and/or human studies do not need further qualification.

DO NOT Qualify Impurities that are Metabolites

A level of a qualified impurity higher than that present in a new drug substance can also be justified based on an analysis of the actual amount of impurity administered in previous relevant safety studies.

If data are not available to qualify the proposed specification level of an impurity, studies to obtain such data may be needed when the usual qualification threshold limits given in Attachment 1 are exceeded.

Changing the threshold levels depends on toxicity

Higher or lower threshold limits for qualification of impurities may be appropriate for some individual drugs based on scientific rationale and level of concern, including drug class effects and clinical experience.

For example, qualification may be especially important when there is evidence that such impurities in certain drugs or therapeutic classes have previously been associated with adverse reactions in patients.

In these instances, a lower qualification

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threshold limit may be appropriate.

Conversely, a higher qualification threshold limit may be appropriate for individual drugs when the level of concern for safety is less than usual based on similar considerations (e.g., patient population, drug class effects, clinical considerations).

Technical factors (manufacturing capability and control methodology) may be considered as part of the justification for selection of alternative threshold limits based on manufacturing experience with the proposed commercial process. Proposals for alternative threshold limits are considered on a case-by-case basis.

The ‘‘Decision Tree for Safety Studies’’ describes considerations for the qualification of impurities when thresholds are exceeded. (Attachment)

In some cases, decreasing the level of impurity below the threshold may be simpler than providing safety data.

Alternatively, adequate data may be available in the scientific literature to qualify an impurity. If neither is the case, additional safety testing should be considered.

The studies desired to qualify an impurity will depend on a number of factors, including the patient population, daily dose, and route and duration of drug administration.

Such studies are normally conducted on the new drug substance containing the impurities to be controlled, although studies using isolated impurities are acceptable.

8. **New Impurities**

During the course of a drug development program, the qualitative impurity profile of the new drug substance may change, or a new impurity may appear as a result of synthetic route changes, process optimization, scale-up, etc.

New impurities may be identified or unidentified.

Such changes call for qualification of the level of the impurity unless it is not more than (>) the threshold values as noted in Attachment 1.

When a new impurity exceeds the threshold, the ‘‘Decision Tree for Safety Studies’’ should be consulted. Safety studies should compare the new drug substance containing a representative level of the new impurity with previously qualified material, although studies using the isolated impurity are also acceptable (these studies may not always have clinical relevance).

10 'RULES TO REMEMBER'

Rule No.1 - Thoroughly evaluate the specified and unspecified impurity profile (i.e. get a absolute baseline profile).

Rule No.2. Treat with CAUTION or REJECT active material with unspecified impurities HIGHER than 0.045 - 0.05% (avoid rounding rule)

Rule No.3. LOOK at impurity profiles of the dedicated synthesis carefully after stressing at accelerated temperatures.

Rule No.4. NDAs have *unique* impurities due to the synthesising and purifying process. LOOK for these 'specified impurities' in the Analytical validation stress study.

Rule No.5. Unspecified impurities (after actual stability testing) should not exceed 0.05% due to the ambiguous wording of the proposed rounding rule.

Evaluate the rounding definition at what point individual unspecified impurities should be rounded identified and qualified.

Rule No.6. Organic impurities are the main focus in impurity profiles (Note: residual solvents have their own guideline and limits).

Rule No.7. Fully evaluate the 'specific impurities' ***and*** the potential impurities (i.e. those impurities which *do* arise and those which *can* arise).

Rule No.8. Always stress the active material *in-house* to see which impurities do occur.

Rule No.9. In active drug development showing unspecified imps. close to 0.1% - Firstly reduce to below 0.05% - before attempting costly identification and qualification.

Rule No.10. REMEMBER an unknown impurity close to 0.08% may grow to >0.1% on stability (ageing). There's no such concept as a safe **unknown** close to 0.1%

Glossary of Terms

Chemical development studies*:* Studies conducted to scale-up, optimize, and validate the manufacturing process for a new drug substance.

Enantiomers*:* Compounds with the same molecular formula as the drug substance, which differ in the spatial arrangement of atoms within the molecule and are non-superimposable mirror images.

Extraneous substance*:* An impurity arising from any source extraneous to the manufacturing process.

Herbal products*:* Medicinal products containing, exclusively, plant material and/or vegetable drug preparations as active ingredients.
In some traditions, materials of inorganic or animal origin may also be present.

Identification threshold*:* A limit above which (>) an impurity needs identification.

Identified impurity*:* An impurity for which a structural characterization has been achieved.

Impurity*:* Any component of the new drug substance that is not the chemical entity defined as the new drug substance.

Impurity profile*:* A description of the identified and unidentified impurities present in a new drug substance.

Intermediate*:* A material produced during steps of the synthesis of a new drug substance that must undergo further molecular change before it becomes a new drug substance.

Ligand*:* An agent with a strong affinity to a metal ion.

New drug substance*:* The designated therapeutic moiety that has not been previously registered in a region or member State (also referred to as a new molecular entity or new chemical entity). It may be a complex, simple ester, or salt of a previously approved drug substance.

Polymorphism*:* The occurrence of different crystalline forms of the same drug substance.

Potential impurity*:* An impurity that, from theoretical considerations, may arise from or during manufacture. It may or may not actually appear in the new drug substance.

Qualification*:* The process of acquiring and evaluating data that establishes the biological safety of an individual impurity or a given impurity profile at the level(s) specified.

Qualification threshold*:* A limit above which (>) an impurity needs to be qualified.

Reagent*:* A substance, other than a starting material or solvent, that is used in the manufacture of a new drug substance.

Reporting threshold*:* A limit above which (>) an impurity needs to be reported.

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Rounding: The process of reducing a result to the number of significant figures or number of decimal places as dictated by the appropriate limit. **For example, a result greater than or equal to (≥) 0.05 and less than (<) 0.15 is rounded to 0.1.** ⊂ ⊂ ⊂

Safety information: The body of information that establishes the biological safety of an individual impurity or a given impurity profile at the level(s) specified.

Solvent: An inorganic or an organic liquid used as a vehicle for the preparation of solutions or suspensions in the synthesis of a new drug substance.

Specified impurity: Identified or unidentified impurity that is selected for inclusion in the new drug substance specifications and is individually listed and limited in order to ensure the safety and quality of the new drug substance.

Starting material: A material used in the synthesis of a new drug substance that is incorporated as an element into the structure of an intermediate and/or of the new drug substance. Starting materials are normally commercially available and of defined chemical and physical properties and structure.

Toxic impurity: An impurity having significant undesirable biological activity. **Unidentified impurity**: An impurity that is defined solely by qualitative analytical properties (e.g., chromatographic retention time).

Unspecified impurity: An impurity that is not included in the list of specified impurities.

CONTACT This DRAFT revised guidance, which updates a guidance on the same topic published in the Federal Register of January 4, 1996 (the 1996 guidance), was prepared under the auspices of the Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–827–5169. Regarding the ICH: Janet J. Showalter, Office of Health Affairs (HFY–20), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–827–0864.

SUPPLEMENTARY INFORMATION:
In recent years, many important initiatives have been undertaken by regulatory authorities and industry associations to promote international harmonization of regulatory requirements.
FDA has participated in many meetings designed to enhance harmonization and is committed to seeking scientifically based harmonized technical procedures for pharmaceutical development.

Global harmonization incentives

One of the goals of harmonization is to identify and then reduce differences in technical requirements for drug development among regulatory agencies. about this draft will be considered by FDA and the Quality Expert Working Group. In accordance with FDA's good guidance practices (62 FR 8961, February 27, 1997), this document is now being called a guidance, rather than a guideline.

Who is this guidance for

The draft revised guidance is intended to provide guidance to applicants for drug marketing registration on the content and qualification of impurities in new drug substances produced by chemical syntheses and not previously registered in the USA.

Who prepared this guidance

This draft revised guidance represents the agency's current thinking on impurities in new drug substances. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both.
Interested persons may submit to the Dockets Management Branch (address above) written comments on the draft revised guidance by September 18, 2000.

Where to get copies

Two copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. A copy of the draft revised guidance and received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday. An electronic version of this guidance is available at http://www.fda.gov/cder/guidance/index.htm or http://www.fda.gov/cber/publications.htm

Who are the Authors

DEPARTMENT OF HEALTH AND HUMAN SERVICES Food and Drug Administration International Conference on Harmonisation [Docket No. 94D–0325] - **Draft Revised Guidance on Impurities in New Drug Substances** AGENCY: Food and Drug Administration, HHS. ACTION: Notice