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Establishing Acceptance Criteria for Approved Impurities in Drug Manufacturing

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Abstract
In the pharmaceutical industry an impurity is defined and recognized the any other organic material besides the drug substance or pharmaceutical ingredients. This paper includes the ongoing impurities in drug development, particularly the API related impurities, for example, degradation related impurities (DRIs) and interaction related impurities (IRIs), may adversely affect the quality, safety, and efficiency of drug products. It is essential that the requirements of regulatory and management strategies are determined. Sources of impurities must also be carefully classified prior to taking subsequent steps, such as developing analytical methods and acceptance criteria. The various international regulatory criteria and requirements are reviewed to bring out the more modifies impurity management outlines. Scheme for the establishment of analytical methods and acceptance criteria of PRIs and DRIs in accordance with the requirements of International Council for Harmonization (ICH) and algorithm to perform the recognition of DPIs by using LC-MS/MS has been proposed.
The kinetic study of compounds to distinguish between DRI and PRIs has been widely used in the field of chemistry. This procedure can also be utilized for the identification of potential fragments.
Keywords: Pharmaceutical Products Impurities Drug manufacturing Patient centric impurity Acceptance.

1. Introduction

Defining impurities according to the United States Pharmacopeial, these are any form of constituent, component, or excipient of a drug substance that is not its chemical entity; for a drug product, any constituent of a drug product that is not its chemical entity.

Classification of Impurities:

Impurities can be classified into the following three categories:
Organic Impurities (Process and Drug Related)
Inorganic Impurities

Residual Solvents

Organic impurities : These are a process based impurities and may occur during the drug manufacturing process and/or storage of the drug substance. They may be identified or unidentified, volatile or nonvolatile, and may include the below:

- Starting materials
- By-products ! Intermediates
- Degradation products
- Reagents, ligands, and catalysts

Inorganic impurities may derive from the manufacturing process. They are normally known and identified and include:

- Reagents, ligands, and catalysts
- Heavy metals
- Inorganic salts Other materials (e.g., filter aids, charcoal)

Residual solvents are typically organic or inorganic liquids. Due to their toxicity, they are commonly used in the manufacturing process.

2. Identification of Impurities in Drug Substances and Products

Drug substance and product organic impurities may include impurities that result from the manufacturing process, and degradation products observed during manufacture and stability studies. Based on a sound scientific appraisal of potential degradation ways in the drug substance and drug product, including those impurities generated when the drug interacts with the environment or when it is sealed with the primary container, impurities must be identified. Impurities observed in stability studies conducted at the recommended storage conditions shall be identified when above the identification verge, which can be established using currently applicable regulations or other scientific means. Impurities present at a level below the identification threshold generally do not need any specific identification.

3. Reporting Impurities and Degradation Products

If the impurity level is above the reporting threshold limit then it's being reported along the analytical method relatively relevant to it. The reporting threshold can be established using currently applicable guidelines or other acceptable scientific means. Quantitative test results shall be reported as numerical values and rounded according to conventional rules. If a change in the method or procedure affects the results reported, the validation information should be linked to the change or procedure used.

The report of every batch of drug substance must include the following:

- Batch identity and size
- Date of manufacture
- Site of manufacture
- Manufacturing process
- Impurity content, individual and total
- Use of batches
- Reference to analytical procedures used

4. Acceptance Criteria for Impurities

The limits are based on the knowledge of the patient's true requirements, which are typically defined by the safety and efficacy of the drug. The use of prior knowledge can help gather additional insight into the criticality of a given product and its impact on patient safety.

Figure-1: The acceptable intake is mostly dependent on the dataset of the compound. If any compound has only a mutagenic alert or is positive in a bacterial reverse mutation assay, then the appropriate TTC based on duration of exposure is used to derive the limit.

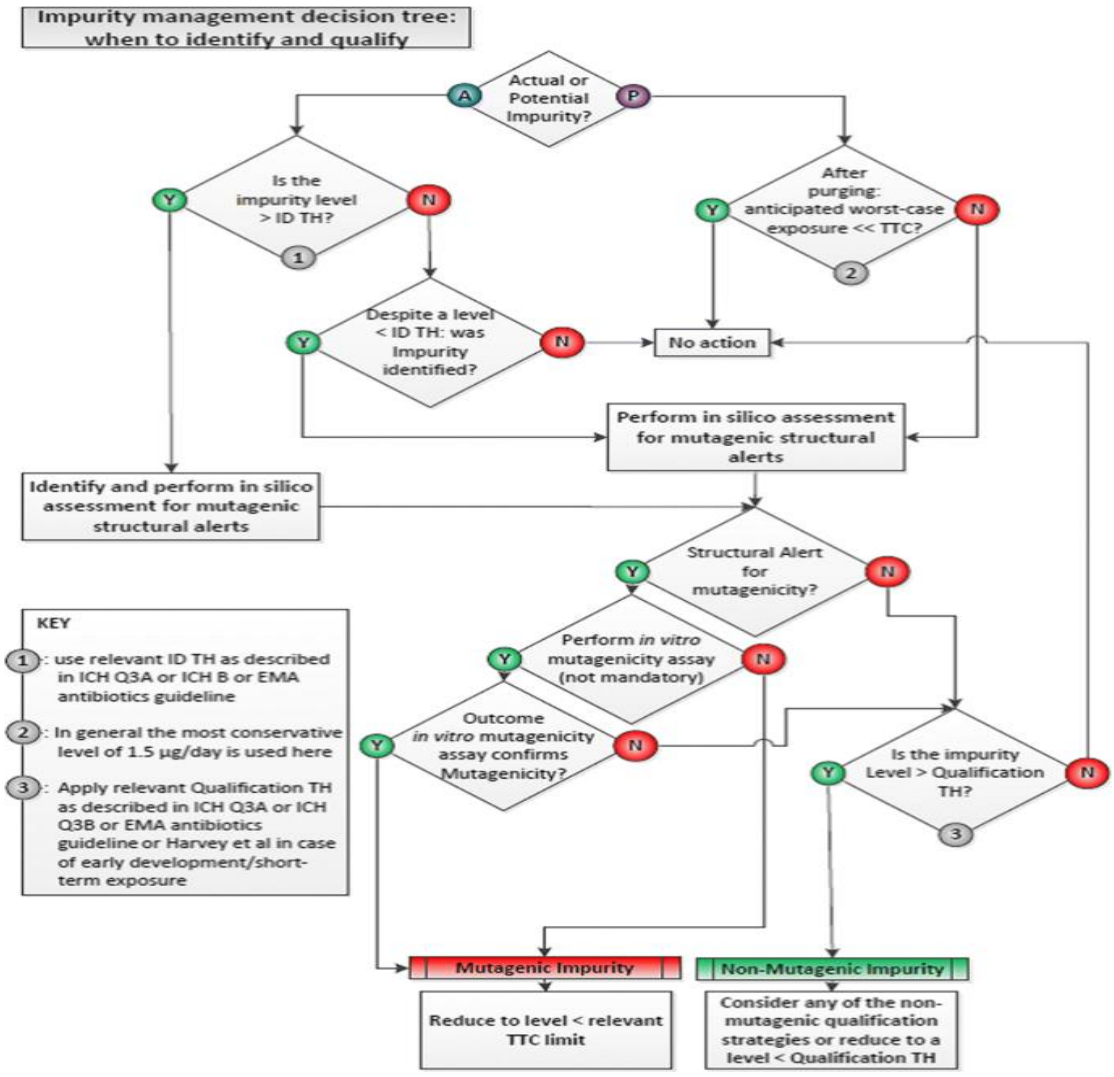

Figure 2-Decision tree on determining the limits for mutagenic and non-mutagenic drug substance impurities

4.1. Generating Limits for Impurities

There are many compound classes with established data sets and common reagents/impurities. In these cases, the toxicity data must be used to derive its limit. Here we will describe how limits are toxicologically developed for these impurities.

ICH Q3C(R6) guidelines speak about the methods for deriving permitted daily exposures (PDEs) for solvents and ICH Q3D describes the same process for elemental impurities . Both approaches are similar but still differ due to the nature of the chemical. The PDE is derived as follows:

PDE=NO(A) EL×BW/F1×F2×F3×F4×F5PDE=NO(A) EL×BW/F1×F2×F3×F4×F5

where

NO(A) EL:

No-observed effect level or No observed adverse effect level

F1:

A factor for extrapolation between species

F2:

A factor of 10 to account for variability between individuals

F3:

A variable factor to consider for toxicity studies of short-term exposure

F4:

A factor that can be applied in cases of severe toxicity, e.g., non-genotoxic carcinogenicity, neurotoxicity, or teratogenicity

F5:

A variable factor that can be applied if the NOEL is not established

BW:

An random body weight of 50 kg (for example)

The PDE for solvents (ICH Q3C) was intended for all routes of administration given the high inhalation and/or oral bioavailability of solvents. The PDE for metals is route specific, with PDEs developed for oral, parenteral, and inhalation routes of administration based on low bioavailability of metals by a particular route and/or the specific toxicity observed from a specific route of administration.

Limits of impurities in degraded drug products:

Each identified degraded product	Not more than 1.0%
Each unidentified degraded product	Not more than 0.50%
Total degraded products	Not more than 2.0%

5. Conclusion

This article provides an outlook on impurities in drug substance and drug product. Impurity profile of pharmaceuticals is getting more significance and drug safety receives more and more attention from literature areas. This article provides the notable information about the impurities types and its classification.

In particular, ICH Q6A clearly states that "specifications should focus on characteristics that have been found to be useful in ensuring the safety and efficacy of the drug substance and drug product"; however, recent negotiations between health authority and applicants (company) related to proposed marketing applications show that on a global level, batch experience, even when limited, plays an overwhelming role in developing impurity acceptance criteria rather than clinical relevance.

During the course of a drug development cycle, the qualitative impurity profile of the drug substance may change or a new impurity may appear, for example, as a result of synthetic route changes, process optimization, or scale-up. New impurities may be identified or unidentified. Changes of this magnitude require consideration of the need to qualify the level of the impurity unless it is below the threshold values mentioned above. When a new impurity exceeds the threshold, the Impurities Decision Tree for generic drug substances should be taken into account. Studies should compare the drug substances containing a representative level of the new impurity with previously qualified material, although studies using the isolated impurity are also acceptable.

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