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STUDY OF IMPURITIES IN NEW DRUG SUBSTANCE

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ABSTRACT

In pharmaceutical world, an impurity is generally considered as any other organic material besides the drug material or active pharmaceutical ingredient (API) that arises out of synthesis. This definition of impurity is broad enough to include degradation products as impurities. The term degradation product is defined as International Conference of Harmonization of technical requirement for registration of Pharmaceuticals for human use. Degradation product: a molecule resulting from a change in the drug substance (bulk material) brought about over time. For the purpose of stability testing of products in this guidance, such changes should occur as a result of processing and storage (e.g., deamidation, oxidation, aggregation, & proteolysis.)

Keywords*:* Deamidation, oxidation, aggregation, proteolysis etc.

Definition:

Impurity is defined as any entity of drug substance (BULK MATERIAL) or drug product (final container product) that is not the chemical entity defined as a drug substance, an excipient, or other additives to the drug product.

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CLASSIFICATION OF IMPURITIES:

1) Organic impurities (process- and drug-related)
2) Inorganic impurities

1) Organic impurities:

Organic impurities can arise during the manufacturing process and/or storage of the new drug substance. They can be identified or unidentified, volatile or nonvolatile, and include:

1) Starting materials
2) By-products
3) Intermediates
4) Degradation product
5) Reagents, ligands, and catalysts

2) Inorganic impurities:

Inorganic impurities can result from the manufacturing process. They are normally known and identified and include:

1) Reagents, ligands and catalysts
2) Heavy metals or other residual metals
3) Inorganic salts
4) Other materials (e.g., filter aids, charcoal)

3) **Description of Impurity type & their source:**

	Impurity type	Impurity source
1	Process-related drug substance	- Organic - Starting material - Intermediate - By-product - Impurity in starting material
2	Process-related drug product	- Organic or inorganic - Reagents, catalysts, etc
3	Degradation drug substance or drug product	- Organic - Degradation products
4	Degradation drug product	- Organic - Excipient interaction

ANALYTICAL PROCEDURES:

The registration application should include documented evidence that the analytical procedures have been validated and are suitable for the detection and quantitation of degradation products (see ICH Q2A and Q2B guidelines on analytical validation). In particular, analytical procedures should be validated to demonstrate specificity for the specified and unspecified degradation products. As appropriate, this validation should include samples stored under relevant stress conditions: light, heat, humidity, acid/base hydrolysis, and oxidation. When an analytical procedure reveals the presence of other peaks in addition to those of the degradation products (e.g., the drug substance, impurities arising from the synthesis of the drug substance, excipients and impurities arising from the excipients), these peaks should be labeled in the chromatograms and their origin(s) discussed in the validation documentation

Analytical method development:

New drug development requires meaningful and reliable analytical data to be produced at various stages of the development.

a) Sample set selection for analytical method development

b) Screening of Chromatographic conditions and Phases, typically using the linear solvent- strength model of gradient elution

c) Optimization of the method to fine-tune parameters related to ruggedness and robustness.

The impurities can be identified predominantaly by following methods;

1) Reference standard method
2) Spectroscopic method
3) Separation method
4) Isolation method

1) Reference standard method:

The key objective of this is to provide clarity to the overall life cycle, qualification and governance of reference standards used in development and control of new drugs. Reference standards serve as the basis of evaluation of both process and product performance and are the benchmarks for assessment of drug safety for patient consumption. These standards are needed, not only for the active ingredients in dosage forms but also for impurities, degradation products, starting materials, process intermediates, and excipients.

2) Spectroscopic methods:

The UV, IR, MS, NMR and Raman spectroscopic methods are routinely being used for characterizing impurities.

3) Separation methods:

The Capillary electrophoresis (CE), Chiral Separations, Gas Chromatography (GC), Supercritical Fluid Chromatography (SFC), TLC, HPTLC, HPLC are regularly being used for separation of impurities and degradation products.

4) Isolation methods:

It is often necessary to isolate impurities. But if the instrumental methods are used, isolation of impurities is avoided as it directly characterizes the impurities.

Generally, chromatographic and non-chromatographic techniques are used for isolation of impurities prior its characterization. The term ‘chromatographic reactor’ refers to the use of an analytical-scale column as both a flow-through reactor, and simultaneously, as separation medium for the reactant(s) and product(s). By using an HPLC, chromatographic reactor approach, the solution-phase hydrolysis kinetics of the Aprepitant (EmendTM) prodrug, fosaprepitant dimeglumine, were investigated. In loratidine, impurity found was ofloratidine, other examples include celecoxib, and amikacin.

Applications:

Numerous applications have been sought in the areas of drug designing and in monitoring quality, stability, and safety of pharmaceutical compounds, whether produced synthetically, extracted from natural products or produced by recombinant methods. The applications include alkaloids, amines, amino acids, analgesics, antibacterials, anticonvulsants, antidepressant, tranquilizers, antineoplastic agents, local anesthetics, macromolecules, steroids, miscellaneous

REFERENCE

1. United States Food and Drug Administration. How drugs are developed and approved-types of applications. 2010. Available from: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/default.htm. Accessed 2013
2. United States Pharmacopeia and National Formulary (USP 36-1159NF 31). Rockville, MD: United States Pharmacopeia Convention; 2013.
3. United States Government. Title 21—Food and Drugs Section 330.1: general conditions for general recognition as safe, effective and not misbranded. Code of Federal Regulations (annual edition); 2011.
4. United States Pharmacopeial Convention. Key Issue: Monograph Modernization. 2012. Available from: http://www.usp.org/usp-nf/key-issues/monograph-modernization. Accessed 2013
5. United States Pharmacopeial Convention. Pharmacopeial Forum (PF). Available from: http://www.usp.org/usp-nf/pharmacopeial-forum. Accessed 2013
6. United States Pharmacopeial Convention. White Paper: Modernization of Organic Impurities Testing in USP Drug Product Monographs. 2013 [cited 2013]; Available from: http://www.usp.org/usp-nf/key-issues/monograph-modernization/organic-impurities-drug-monographs/white-paper-modernization-organic-impurities.
7. United States Pharmacopeial Convention. Over-the-Counter (OTC) Drug Substances and Drug Products Workshop. 2011. Available from: http://www.usp.org/meetings-courses/workshops/over-counter-otc-drug-substances-and-drug-products-workshop. Accessed 2013.