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IMPURITY PROFILING AND QUALITY BY DESIGN

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ABSTRACT

Impurity profiling is the process of acquiring and evaluating data that establishes biological safety of an individual impurity. There is no clear definition for impurity in the pharmaceutical world. Impurity profiling includes identification, structure elucidation and quantitative determination of impurities and degradation products in bulk drug materials and pharmaceutical formulations. Impurity profiling has gained importance in modern pharmaceutical analysis due to the fact that unidentified, potentially toxic impurities are hazardous to health and in order to increase the safety of drug therapy, impurities should be identified and determined by selective methods. Identification of impurities is done by variety of Chromatographic and Spectroscopic techniques, either alone or in combination with other techniques. The advent of hyphenated techniques has revolutionized impurity profiling, by not only separation but structural identification of impurities as well. The present review covers various aspects related to the analytical method development for impurity profiling of an active pharmaceuticals. Impurity profiling encounters problems in bulk drugs since it assists in enhancing bulk drug quality ultimately benefiting patient.

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INTRODUCTION

The bulk drug industry forms base of all pharmaceutical industries as it is the source of active pharmaceutical ingredients (APIs) of specific quality. Over the last few decades much attention is paid towards the quality of pharmaceuticals that enter the market. The major challenge for both bulk drug industries and pharmaceutical industries is to produce quality products. It is necessary to conduct vigorous quality control checks in order to maintain the quality and purity of output from each industry. Purity of active pharmaceutical ingredient depends on several factors such as raw materials, their method of manufacture and the type of crystallization and purification process. Concept about purity changes with time and it is inseparable from the developments in analytical chemistry. The pharmacopoeias specify not only purity but also puts limits which can be very stringent on levels of various impurities. Modern separation methods clearly play a dominant role in scientific research today because these methods simultaneously separate and quantify the components hence making the separation and characterization of impurities easier. Impurities in pharmaceuticals are unwanted chemicals that remain with the Active Pharmaceutical Ingredients (APIs) or develop during formulation or develop upon ageing of both APIs and formulated APIs to medicines. The presence of these unwanted chemicals even in small amounts may influence the efficacy and safety of the pharmaceutical products. Different pharmacopoeias such as British pharmacopoeia (BP) and the United States pharmacopoeia (USP) are slowly incorporating limits to allowable levels of impurities present in the APIs or formulations. The International Conference on Harmonization (ICH) has published guidelines on impurities in new drug substances, products and residual solvents. The main reasons for the increasing interest of drug manufacturers and drug registration authorities in the impurity profiles of bulk drug substances are as follows:

a. In the course of the development of a new drug or a new technology for manufacturing an existing drug it is essential to know the structures of the impurities: by possessing the information synthetic organic chemists are often able to change the reaction conditions in such a way that the formation of the impurity can be avoided or its quantity reduced to an acceptable level.

b. Having suggested structures for the impurities, they can be synthesized and thus provide final evidence for their structures previously determined by spectroscopic methods.

c. The material synthesized can be used as an 'impurity standard' during development of a selective method for the quantitative determination of the impurity and the use of this method as part of the quality control testing of every batch.

d. In case of major impurities the synthesized or isolated material can be subjected to toxicological studies thus greatly contributing to the safety of drug therapy.

e. For drug authorities the impurity profile of a drug substance is a good fingerprint to indicate the level and constancy of the manufacturing process of the bulk drug substance.

Regulatory Guidelines on Impurities in an Active Pharmaceutical Ingredient:

Ethical, economic and competitive reasons as well as those of safety and efficacy support the need to monitor impurities in drug products. However monitoring impurities and controlling these impurities mean different things to different people or to the same people at different times, even those in the pharmaceutical sciences and industry. A unified terminology is necessary to assure that everyone uses the same vocabulary when addressing questions related to impurities. The United States Food and Drug Administration (US FDA) have endorsed the guidance prepared under the guidance of the International Conference of harmonization (ICH). The ICH guideline for impurities in pharmaceuticals was developed with joint efforts of regulators and industry representatives from the European Union (EU), Japan and United States and it has helped to ensure that different regions have consistent requirements for the data that should be submitted to various regulatory agencies. The guidelines not only aid the sponsors of New Drug Applications (NDA) or Abbreviated New Drug Application (ANDA) with the type of information that should be submitted with their applications, but also assist the FDA reviewers and field investigators in their consistent interpretation and implementation of regulations1-2. The various regulatory guidelines regarding impurities are as follows:

1. ICH guidelines "stability testing of new drug substances and products"- Q1A
2. ICH guidelines "Impurities in New Drug Substances"- Q3A
3. ICH guidelines "Impurities in New Drug Products"- Q3B
4. ICH guidelines "Impurities: Guidelines for residual solvents"- Q3C
5. US-FDA guidelines "NDAs -Impurities in New Drug Substances"
6. US-FDA guidelines "ANDAs - Impurities in New Drug Substances
7. Australian regulatory guideline for prescription medicines, Therapeutic Governance Authority (TGA), Australia.

Rationale for Reporting of Impurities in Active Pharmaceutical Ingredient:

The setting of limits for allowable impurities in bulk drugs is a complex process which depends on number of factors like toxicology of impurities related to drug, route of administration, daily dose, target population, source of drug substance and duration of therapy. The basis behind setting limits on level of impurities is that impurities in drug substance must be controlled to ensure the safety and efficacy and quality of API throughout its development and use as a product, as some of these impurities might possess certain undesirable toxicological potential.

The profile of impurities in a new drug substance may change for a variety of reasons, such as process scale-up changes, synthetic route change and changes made to key intermediates. ICH decision tree help to classify quality and select limits for New Molecular Entities (NMEs). If an impurity exceeds the qualification threshold listed in Table 1.1, studies are needed to qualify that impurity in drug substances. 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

Table1- Threshold values.

Maximum daily dose(a)	Reporting threshold (b,c)	Identification threshold (c)	Qualification threshold
2gm/day	0.05%	0.1% or 1mg/day intake (whichever is less)	0.15% or 1mg/day intake (whichever is less)
2gm/day	0.03%	0.05%	0.05%

a. The amount of drug substance administered per day.
b. Higher reporting thresholds should be scientifically justified.
c. Lower thresholds can be appropriate if the impurity is unusually toxic.

SOURCES AND TYPES OF IMPURITIES:

The impurities usually encountered in pharmaceuticals are synthesis-related, formulation-related or degradation-related. There are two types of impurities in medicines**:**

1) Impurities associated with active pharmaceutical ingredients (APIs).
2) Impurities that are formed during formulation and or with ageing or that are related to the formulated forms. According to ICH guidelines, Impurities associated with APIs are classified into the following categories:

- Organic impurities (Process and Drug related)
- Inorganic impurities
- Residual solvents

Organic impurities:

Organic impurities may arise during the manufacturing process and/or storage of the drug substance. They may be identified or unidentified, volatile or non-volatile including starting materials, by-products, intermediates, degradation products, reagents, ligands and catalysts. Starting materials or intermediates are the most common impurities found in every API unless a proper care is taken in every step involved in throughout the multi-step synthesis.

Inorganic impurities:

Inorganic impurities may also arrive from manufacturing processes used for bulk drugs.They are normally known and identified and include the following:

Reagents, ligands and catalysts-

The chances of presence of these impurities are rare. However, in some processes, these could create a problem unless the manufacturer takes proper care during production.

Heavy metals-

The main sources of heavy metals are the water used in the processes and the reactors (if stainless steel reactors are used), where acidification or acid hydrolysis takes place. These impurities of heavy metals can easily be avoided using demineralized water and glass-linked reactors.

Other materials (filter aids, charcoal)-

The filters or filtering aids such as centrifuge bags are routinely used in bulk drug manufacturing plants and in many cases activated carbon is also used. The regular monitoring of fibers and black particles in the bulk drugs is essential to avoid these contaminants.

Residual solvents:

Residual solvents are organic or inorganic liquids used during the manufacturing process. It is very difficult to remove these solvents completely by the workup process. Some solvents that are known to cause toxicity should be avoided in the manufacturing of bulk drugs. Depending upon the possible risk to human health, residual solvents are divided in three classes.

a)**Class I:** Solvents like benzene (2 ppm limit) and carbon tetrachloride (4 ppm limit) should be avoided.
b)**Class II:** Methylene chloride (600 ppm limit), methanol (3000 ppm limit), pyridine (200 ppm limit), toluene (890 ppm limit) and acetonitrile (410 ppm limit) are the most commonly used solvents.
c)**Class III:** Acetic acid, acetone, isopropyl alcohol, butanol, ethanol and ethyl acetate have permitted daily exposures of 50 mg or less per day.

Formulation related impurities:

Apart from bulk drug related-impurities the formulated form of API may contain impurities that are formed in various ways.

Method related impurities:

Some impurities are generated during the formulation process either due to exposure to heat, light, change of pH, solvents etc. (e.g. Formation of impurity 1-(2,6- dichlorophenyl)-indolin-2-one on autoclaving of diclofenac sodium).

Environment related impurities:

1)Due to exposures to adverse temperatures (e.g. Vitamins as drug substances are very heat- sensitive and degradation frequently leads to loss of potency in vitamin products, especially in liquid formulations)

2)Due to exposure of light specially UV light (e.g. Ergometrine as well as methylergometrine is unstable under tropical conditions such as light and heat)

3)Humidity (Humidity is considered detrimental for hygroscopic products e.g.Aspirin and Ranitidine)

ISOLATION AND IDENTIFICATION OF IMPURITIES IN ACTIVE PHARMACEUTICAL INGREDIENTS

The process of identification of impurities and/or degradants begins early in drug development. The first step of the process is to determine at what level the unknown impurity is present. According to the ICH guidelines on Impurities in New Drug Substances, '*The studies conducted to characterize the structure of actual impurities present in the new drug substance at a level greater than 0.1% (depending on the daily dose, calculated using the response factor of the drug substance) should be described. Note that all specific 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 the identification of an impurity is not feasible, a summary of the laboratory studies demonstrating the unsuccessful effort should be included in the application.'* Identification of impurities below the 0.1% level is generally not considered to be necessary unless the potential impurities are expected to be unusually potent or toxic.

Therefore it is imperative to determine the level of the unknown impurity early in the process. If the unknown impurity is below 0.1% threshold, then a discussion will need to take place among the project team members in order to determine if isolation and identification is necessary. However, if the unknown is at or above the 0.1% limit, then effort should be put for isolation and identification.

Methods for Isolation and Identification of Impurities

A number of methods can be used for isolating impurities. Three of the most utilized techniques are thin-layer chromatography (TLC), flash chromatography (column chromatography) and preparative high performance liquid chromatography (HPLC).

The actual technique to be used depends upon the nature of the impurity and/or degradant, including the amount present in the original material from which it must be isolated.

Extraction techniques are used some times for isolation of impurities, on the basis of difference in the solubility of impurity and drug substance in various solvents. It is possible to extract impurities selectively on the basis of acidity, basicity or neutrality of impurities in question. The extraction procedure usually involves liquid-liquid extraction where one phase is aqueous while the other is non-polar organic phase. By appropriate adjustment of pH of aqueous phase one can extract acidic, basic or neutral impurities. The technique work well when a few impurities are present and their polarity or pKa of impurities is sufficiently different from that of drug substance20. If necessary, further separations can be achieved by chromatographic methods. Other methods which are used for isolation of impurities include Solid Phase Extraction methods (SPE), Supercritical Fluid Extraction (SFE), Capillary Electrophoresis (CE) and Supercritical Fluid Chromatography (SFC). Some of the techniques listed above like SPE and SFE are normally used for sample clean up before analysis. Capillary electrophoresis is largely used for analysis of impurities in protein pharmaceuticals.

Different spectroscopic techniques like UV-spectroscopy, IR-spectroscopy, Mass Spectrometry and Nuclear Magnetic resonance Spectroscopy are used in identification of isolated impurities. Structural elucidation of impurities using these spectroscopic techniques is known as characterization of impurities.

CONCLUSION

Impurity profiling of a substance under investigation gives maximum possible account of impurities present in it. The establishment of guidelines for impurity levels in drug substances and products provides the quality criteria for manufacturers. The key aspect is that the impurity profiling of a new chemical entity must be shown to be qualified. With a qualification threshold of 0.1%, or lower for high dose compounds, the pharmaceutical analyst must give careful thought to their analytical technology.

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