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REVIEW ARTICLE

A Review on Significances of Impurity Profiling

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ABSTRACT:

In pharmaceutical world, an impurity is considered as any other organic or inorganic material, besides the drug substance, or ingredients, that arise out of synthesis or unwanted chemicals that remains with API's. The impurity may arise either during formulation, or upon aging of both API's and formulated API's in medicines. Nowadays, the focus has been definitely shifted from the 'purity profile' to 'impurity profile' (IMPs) that are present in the drug substance and degradation products (DP) including genotoxic impurities (GITs) in the finished pharmaceutical products. The presence of such superfluous impurities may affect the ADMET properties of drugs in human body. The control of impurities in formulated products and API's were regulated by different regulatory authorities like ICH, USFDA, FDA, Canadian Drug and Health Agency are emphasizing on the purity profile and the identification of impurities in API's. Thus enlightening the need of impurity profiling of drug substances or drug products in pharmaceutical research this review focuses on various analytical methods and advances in the analytical techniques used for their identification as well as qualification of the impurities present in pharmaceutical products. There are different methods for detecting and characterizing the impurities with TLC, HPLC, HPTLC, etc. Impurity profiling study in the recent pharmaceutical outline and its importance is growing day-by-day. The present review covers the various strands related to the analytical method development for impurity profiling of API and pharmaceutical products.

KEYWORDS: Impurity profiling, Identification, ICH guidelines, Degradation, Analytical method development.

INTRODUCTION:

In pharmaceutical industries, the bulk manufacturing industry that forms the base as it is the source of API's of specific quality. Drug formulations contain Active pharmaceutical Ingredients and excipients. APIs present in the formulation contain some undesired impurity, which also affects the purity of the APIs. Therefore, along with percent (%) purity, impurity profile is also needed to be carried out of all the APIs.

Impurities in the pharmaceuticals are the surplus chemicals that stay behind within the active pharmaceutical ingredients or develop during formulation or upon aging of both active content as well as formulated active ingredients to medicines [2]. The presence of such unwanted chemicals even in small amounts may affect the efficacy and safety of the pharmaceutical products. Impurity profiling deals with identification, recognition, structure elucidation and quantitative determination of organic, inorganic impurities also the residual solvents in bulk drugs and pharmaceutical products. Over the last few decades much attention is paid towards the quality of pharmaceutical products that enter the market. It is therefore, necessary to keep vigorous quality control checks in order to

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maintain the quality and purity profile of output of each industry [3]. Different pharmacopoeias such as Indian pharmacopoeia (IP), British pharmacopoeia (BP) and the United States pharmacopoeia (USP) are slowly incorporating limits to acceptable levels of impurities present in APIs or formulation [3]. The International conference on Harmonization (ICH) has published various guidelines on impurities in new drug substances or drug products and residual solvents. The various analytical techniques approaches for isolation and identifying the process related to impurities and degradation products in drug substance or products are Mass spectroscopy (MS), Nuclear magnetic spectroscopy (NMR), Gas chromatography (GC), Capillary electrophoresis, High performance liquid chromatography (HPLC), etc. has been established to review a summary of the various problem and the other possibilities offered by modern analytical chemistry [1,6].

Impurity profiling:

There is no pinpoint definition for impurity profile. It gives an account on impurities that are present in the bulk and finished drug substance or product. It helps in identifying and quantifying the impurities present in the typical batch of API or pharmaceutical formulation produced by a specific controlled production process [1]. It gives maximum possible types of impurities present in drug substance or drug products (API) and in pharmaceutical formulations. It also estimates the actual quantity of different kinds of impurities present in it.

ICH Guidelines for impurity profiling:

It is now getting an important critical attention from regulatory authorities. The International Conference on Harmonization has published various guidelines on impurities in drug substances and drug products as well as residual solvents [3].

- 1) Q1A-“stability testing of new drug substances and products”
- 2) Q3A (R2) - “Impurities in New Drug Substances”
- 3) Q3B (R2) - “Impurities in New Drug Products”
- 4) Q3C (R5) - “Impurities: Guidelines for Residual Solvents”

According to the ICH guidelines on impurities in new drug products, the identification of impurities below 0.1% level is not considered to be necessary, unless potential impurities are expected to be usually potent or toxic. Limits for impurities in drug substances are shown in table 1 [2, 8].

Table1: limits for impurities in new drug substance

Maximum daily dose	Reporting Threshold	Identification Threshold	Qualification Threshold
2g/day	0.05%	0.10% or 10 mg per day intake(whichever is lower)	0.15% or 10 mg per day intake(whichever is lower)
>2g/day	0.03%	0.05%	0.005%

Classification of impurities:

The classification of impurities as per ICH is as followed [3] :

- 1) Organic impurities (process and drug related)
- 2) Inorganic impurities (Reagents, ligands, catalysts)
- 3) Residual solvents (volatile solvents)

Organic impurities:

These types of impurities arise mainly during manufacturing process and /or during storage of the drug substance. These include following impurities:

Starting materials or intermediates:

The impurities that arise from starting materials or intermediates is found in every API unless proper care is not taken in every step involved in the multi-step synthesis. Although the end product are always washed with solvents, there is always chance that the residual unreached starting material remain, except the manufactures are very careful about the impurities [3-4]. E.g. In the synthesis of Baclofen, the last step carried out with Glutarimide which on reaction with sodium hydroxide/sodium hydrochloride at room temperature yields an impurity i.e. p-chlorophenylglutaric acid [7].

Degradation products:

During manufacturing of the bulk drugs degradation of the end products results in the formation of impurities. Degradation products that arise during the synthetic process, storage, manufacturing of dosage form and aging. E.g. Penicillin and cephalosporin are classic examples for impurities from degradation products [3].

By-products:

In synthetic organic chemistry getting an single end-product with 100% yield is very rare. There is always a chance of having a by-product [3-4,17]. Because they can be formed through variety of side reactions such as partial reaction, unskilful reaction, over reaction, isomerization, rearrangement or unwanted reactions between starting or intermediate material with chemical reagent or catalysts. E.g. In case of paracetamol bulk production, diacetylated paracetamol may forms as a by-product [3].

Inorganic impurities[3-4,17]:

Inorganic impurities are normally detected and quantified using different pharmacopoeia or other

appropriate standards. Inorganic impurities may also derive from the manufacturing processes used in bulk drugs formulations. These type of are normally known and identified and include the following:

Reagents, ligands and catalysts:

The chances of having these type of impurities are very rare, however, in some processes these could create a problem unless the manufacturers himself take proper care during production.

Heavy metals:

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

Other materials (e.g., filter aids, charcoal etc.):

The filters or filtering aids such as centrifuge bags have been routinely used in the bulk drugs manufacturing plants and in many cases, activated carbon is also used. The regular observation of fibers and black particles in the bulk drugs is essential to avoid these type of contaminations.

Residual solvents:

Residual solvents are organic, inorganic volatile chemicals that are used or produced in the manufacture of drug substances or excipients, or in the manufacturing of drug products. Residual solvents are difficult to remove completely [4, 8]. However, efforts have been taken to remove them completely. The residual solvents are classified as follows:

Class 1 solvents:

These types of solvents should be avoided in pharmaceutical products known human carcinogens and are strongly suspected human carcinogens and environmental hazards. Solvents to be avoided in pharmaceutical products are listed below in table 2 [8].

Table 2: Solvents to be avoided in pharmaceutical products

Solvents	Concentration limit (ppm)	concern
Benzene	2	Carcinogenic
Carbon tetrachloride	4	Toxic
1,1-Dichloro ethane	8	Toxic
1,1,1-Trichloroethane	1500	Environmental hazard

Class 2 solvents:

Non-genotoxic animal carcinogens or possible causative agents of other irreparable toxicity such are neurotoxicity or teratogenicity. The solvents to be limited in the pharmaceutical products in table 3 [8].

Table 3: Solvents to be limited in pharmaceutical products

Solvents	Permitted daily exposure (mg/day)	Concentration limit (ppm)
Acetonitrile	4.1	410
Chlorobenze	3.6	360
Chloroform	0.6	60
cyclohexane	38.8	3880
1,2-Dichloroethane	18.7	1870

Class 3 solvents:

These solvents are less toxic in acute or minuscule term studies and negative in genotoxic studies. The amount of these residual solvents of 50 mg or less would be acceptable. E.g. for this class of solvents are Acetic acid, Acetone, Anisole, 1-Butanol, 2-butanol, Ethanol, Ethyl acetate [3, 8].

Class 4 solvents:

The solvents of this class may be interesting to manufacturers of the excipients, drug substances or drug products. But there was no sufficient toxicological data on which to base a permitted daily exposure was found. E.g. for this class of solvents are 1, 1-Diethoxy propane, 1-Dimethoxy propane, Isooctane [3, 8].

Formulation related impurities:

A number of impurities can arise out of inert ingredients used to formulate a drug substance. The formulation related impurities are classified as follows [2-3]:

- a) Method related
- b) Environmental related The primary environmental factors that can reduce stability include the following factors:
- c) Exposures to adverse temperatures
- d) Light- especially UV light
- e) humidity
- f) Dosage form related
- g) Mutual interaction amongst ingredients
- h) Ester hydrolysis
- i) Functional group related typical degradation
- j) Oxidative degradation
- k) Hydrolysis
- l) Photolytic cleavage
- m) Decarboxylation

Degradation products and its qualification [8, 16]:

Degradation product is an impurity resulting from a chemical change in the drug substance brought about during manufacturing and/or storage of the new drug product by the effect of light, temperature, pH, or by the reaction with an excipient and/or the immediate container closure system. According to ICH guidelines Qualification is defined as the process to determine and evaluating the data that establishes the biological safety of an individual degradation product that are present in a

profile at level(s) specified. Hence for any degradation product present in the new drug substance should be adequately tested in safety and clinical studies for their qualification. An impurity is considered to be qualified based upon the acceptance criteria of one or more of the following conditions they are as follows:

a) When observed level and proposed accepted criteria does not exceed the level observed in FDA approved human drug product.

b) When the impurity is a significant metabolite of the drug substance.

c) When the observed level and the predetermined accepted level for the impurity is adequately justified in the scientific literature.

d) When the predetermined and the accepted level for impurity does not exceed the level that has been sufficiently evaluated in comparative in-vitro genotoxic studies.

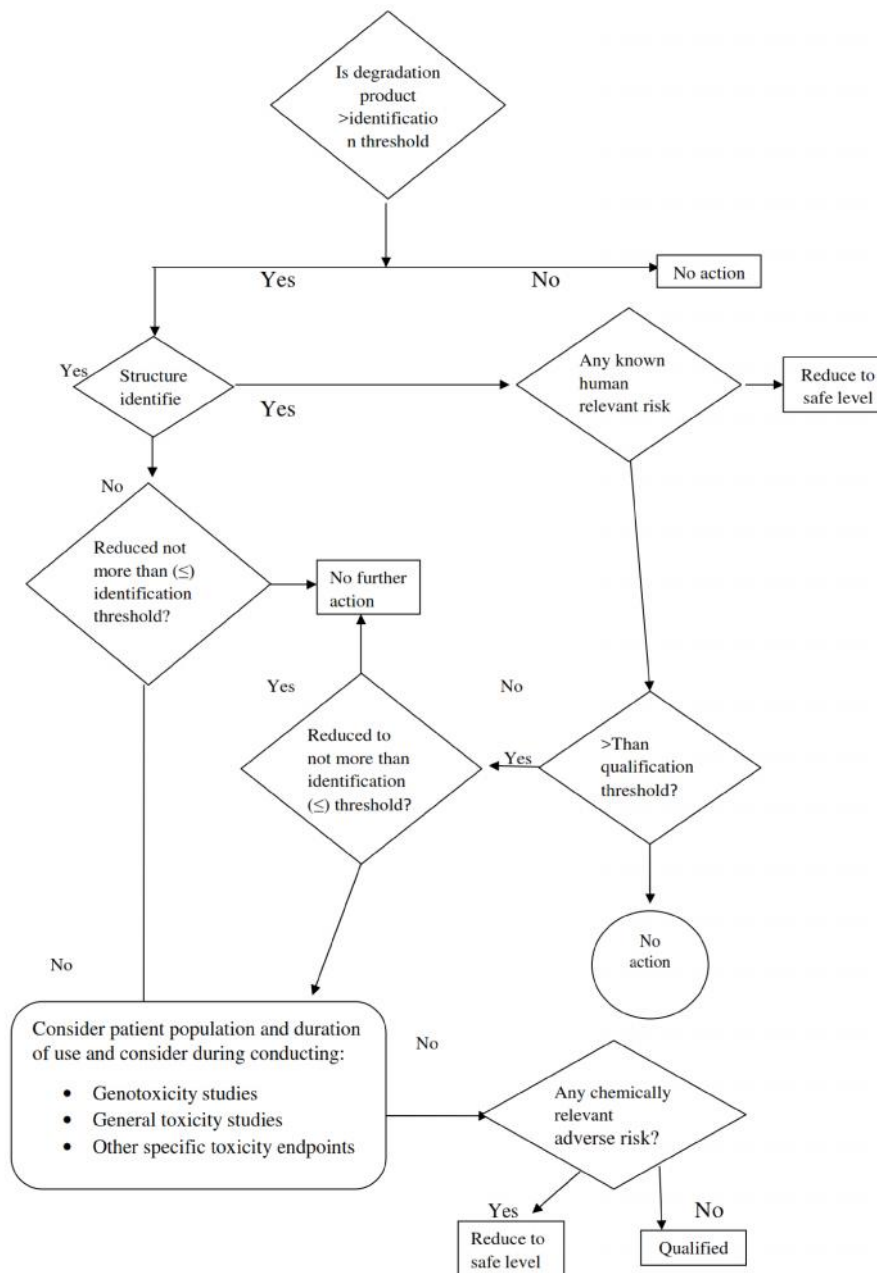


Chart No. 1 : The Decision tree for identification and Qualification of a Degradation product

Recall of products due to degradation:

During qualification of drug substance or drug products certain drugs may undergo degradation which are recalled by the USFDA due to presence of certain IMPs/DPs example of such degradation products are as follows [5]:

1. Adagen injection 250 units/ml, 1.5 ml single-dose vials/carton (250 cartons) were recalled during routine stability testing, levels of IMP were out of specification.
2. Azelastin hydrochloride ophthalmic solution, 0.05 % (sterile), 6 ml bottles (155,363 bottles) were recalled during analysis of 18 months controlled stability samples.
3. Cycloprirrox Gel, 0.77%, 45 g tube (24,664 tubes) were recall due to unspecified IMP at the 9 month stability test station.
4. Migergot Rectal suppositories USP (10,968 boxes) product were recall due to out of specification for a known DP, ergotamine.
5. A recall of nelfinavir mesylate product from the market due to conversion of mesylate to ethyl methane sulfonate, a GTI owing to interaction with residual ethanol that was used for cleaning manufacturing surfaces.
6. Fluocinonide Topical Solution USP, 0.05% in 60 mL bottles, was recalled in the United States because of degradation/impurities leading to sub-potency
7. A report is available where varnish applied to label migrated into the container resulting in the presence of a leachable in the product.

Isolation [3-6]:

It is frequently necessary to isolate the impurities. But if in case instrumental methods are used, the isolation of impurities is avoided as it directly leads to the characterization of impurities. Generally, chromatographic and non-chromatographic techniques are been used for isolation of impurities prior its characterization. The term 'chromatographic reactor' refers for the use of an analytical scale column as both a flow through reactor and simultaneously as separation medium for the reactant and product. By using HPLC, the solution phase hydrolysis kinetics of Aprepitant prodrug, for aprepitant dimeglumine, were investigated. A list of methods that can be used for isolation of impurities are liquid-liquid extraction, solid-phase extraction method, supercritical fluid extraction, column chromatography, flash chromatography, thin layer chromatography, capillary electrophoresis (CE), Accelerated solvent extraction methods.

Characterization Methods:

Highly sophisticated instrument such as MS attached to HPLC or GC are inevitable tool in the identification of minor components such as drugs, impurity, degradation products, metabolites, etc. in various matrices. For such

impurities characterization different techniques are used which are as follows.

NMR:

The ability of the NMR is use to provide information regarding the specific bond structure and the stereochemistry of molecules of pharmaceutical interest has made it a powerful analytical instrument for identification and structural elucidation. The ability of NMR base diffusion coefficient determination to distinguish between monomeric and dimeric substances was validated using a standard mixture of authentic mixture which contains both monomers and dimers. However, NMR is been used as less traditional method compared to other analytical techniques. Conventionally sample requirements for NMR is in order of 10 mg, as compared with MS, which requires less than 1 mg [2-6].

MS

It has a significant increasing impact on the pharmaceutical development processes over past few decades. Mass spectroscopy have afforded new opportunities for monitoring, qualification and characterization of drug related substances and products in API's and pharmaceutical formulations. If single method fails to provide the necessary information orthogonal coupling of chromatographic techniques is been done such as HPLC-TLC and HPLC-CE is been used for routine QC (Quality control) use [2-6].

Hyphenated methods

- LC-MS-MS
- HPLC-DAD-MS
- HPLC-DAD-NMR-MS
- LC-MS

CONCLUSION:

This review provides a perspective on impurity profiling in drug substance and drug product. Impurity profiling in pharmaceutical world is an increasing importance and drug safety receives more and more attention from public and media. This article provides valuable information regarding the types of impurities and its various techniques for isolation and characterization, various analytical techniques for determination, identification and qualification of impurities and critical factors ha to be considered while the preparation of the bulk drugs.

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