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REGULATORY ASPECTS FOR IMPURITY PROFILING OF PHARMACEUTICAL PRODUCTS: AN OVERVIEW

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ABSTRACT: Pharmaceutical impurities are the organic and inorganic unwanted chemicals which are found in active pharmaceutical ingredient after synthesis or develop during formulation development. These impurities severely affect the safety and efficacy of developed pharmaceutical product. Impurity profiling detects and quantifies the levels of organic and inorganic impurities and thereby helps in better monitoring of quality, stability and safety of pharmaceutical products. Regulatory bodies worldwide are serious towards presence of impurities and impurity profiling has thus become an important step in filling drug dossiers. The ICH guidelines on impurity have clearly defined the levels of toxic impurities and have become benchmark in establishing impurities in pharmaceutical drug products. The present article summarizes the concept of impurity profiling and also presents a case study on impurity profiling of methamphetamine hydrochloride to illustrate its significance. Further a case study is presented on quantification of active pharmaceutical ingredient and impurities in sildenafil citrate purchased via internet and its relative outcomes.

INTRODUCTION: In the present era, there has been an ever increasing interest in impurity profiling in the pharmaceutical industry. This is due to the fact that even trace level of impurities can adversely affect both the safety and efficacy of the pharmaceutical drug product. Some of the impurities formed can also be mutagenic or teratogenic. Thus, there is a need for controlling the level of impurities present within limits in both drug substances and drug products. ICH has published guidelines on the impurities in new drug substances, new drug products, residual solvents and elemental impurities.¹

Impurity: ICH defines impurities as for pharmaceutical products; the control of impurities is a critical issue for pharmaceutical Industry. Impurities are any organic material besides the drug substances and excipients may be described as impurities. Impurities in pharmaceuticals are the unwanted chemicals that remain with the active pharmaceutical ingredients (APIs), or develop during formulation or upon aging of both API 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.²

Impurity profiling:

There is no accurate definition for impurity profile. It gives an accounting of impurities present in it. Impurity profile is a description of the identified and unidentified impurities existing in a typical batch of API (Active Pharmaceutical Ingredient)

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produced by a precise controlled production process. It includes the identity or any qualitative analytical determination (*e.g.* retention time), the range of each impurity identified and type of each identified impurity. Impurity profile of a substance under investigation gives maximum possible types of impurities present in it. It also estimates the actual amount of different kinds of impurities present in it. For each API there should be an impurity profile describing the identified and unidentified impurities present in a typical batch. The impurity profile is normally dependent upon the process or origin of the API.³ The general scheme for impurity profiling is shown in **Fig. 1**.⁴ Regulatory authorities are also emphasising on not

only the purity profile but on impurity profiling (identification, isolation and characterization of impurity) for the licensing purpose and regulatory related issues for particular drug substance and drug product. Different pharmacopoeias like British Pharmacopoeia (BP), European Pharmacopoeia (EP), Indian Pharmacopoeia (IP), Japanese Pharmacopoeia (JP) and United States Pharmacopoeia (USP) are also revising their monographs for the drug substances and drug products every year by introducing the limits for the different types of impurities.⁵ The Classification of impurities as per different terminologies is shown in **Fig. 2**.^{6,7}

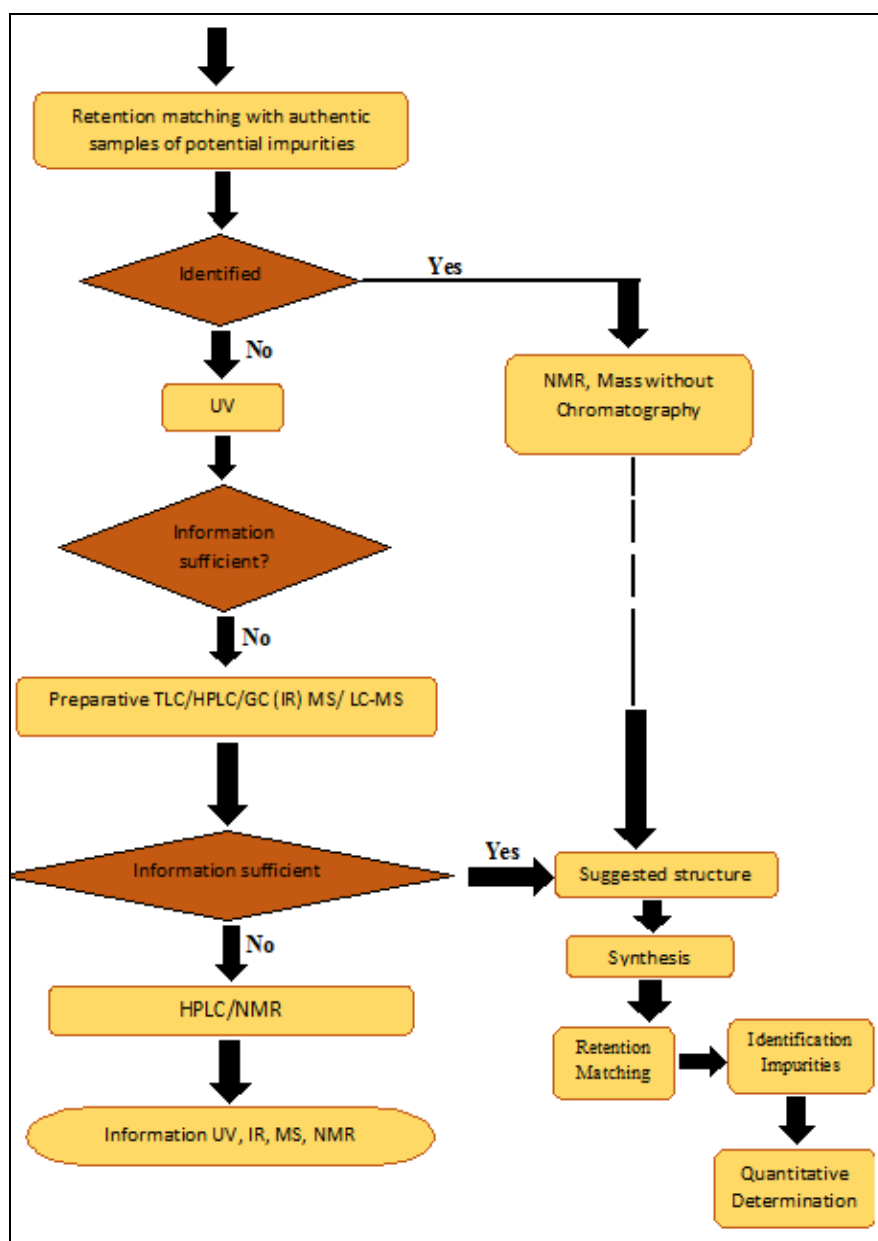


FIG. 1: GENERAL SCHEME FOR IMPURITY PROFILING

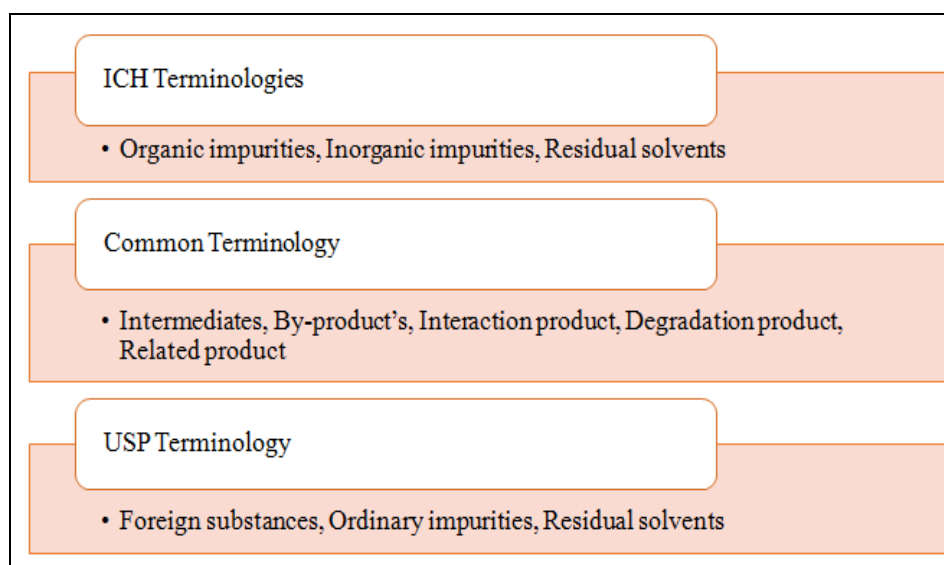


FIG. 2: CLASSIFICATION OF IMPURITIES AS PER DIFFERENT TERMINOLOGIES

Sources of impurities: Compound investigated in drug discovery leads to a significant analytical challenge for the characterization, quantization, and detection of the compounds.⁸ Fig. 2 summarizes all classes of impurities. Following are the various sources of impurities in pharmaceutical products:

- Organic impurities (process- and drug-related): They can be identified or unidentified, volatile or non-volatile, and it's include: Starting materials, By-products, Intermediates, Degradation products, Reagents, ligands and catalysts.
- Inorganic impurities: They are normally identified and it's include: Reagents, ligands and catalysts, Heavy metals or other residual metals, Inorganic salts Other materials (*e.g.*, filter aids, charcoal)
- Miscellaneous Impurity: They are inorganic or organic liquids used as vehicles for the preparation of solutions or suspensions in the synthesis of a new drug substance. They are normally polymorphic forms and enantiomeric impurity.⁹

Global Regulatory Guidelines: The significant global guidelines on impurity and impurity profiling are as follows:

ICH (International Council on Harmonisation): The International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) is a project that brings together the regulatory authorities of Europe, Japan and the United States and experts

from the pharmaceutical industry in the three regions to discuss scientific and technical aspects of pharmaceutical product registration.¹⁰

The Guidelines of impurity profiling in ICH are mentioned below.

- A. Impurities in New Drug Substances Q3A (R2)
- B. Impurities in New Drug Products Q3B (R2)
- C. Impurities: Guideline for Residual Solvents Q3C (R5)
- D. Guideline for Elemental Impurities Q3D

(A) Impurities in New Drug Substances Q3A (R2): The main objective of the Q3A (R2) guideline is to provide direction to registration applications on the content and qualification of impurities in new drug substances produced by chemical synthesis. Biological/biotechnological, peptide, oligonucleotide, radiopharmaceutical, fermentation product and semi-synthetic products derived there from, herbal products, and crude products of animal or plant origin are not covered by this guideline.¹¹

(B) Impurities in New Drug Products Q3B (R2): The main objective of the Q3B (R2) guideline is to provide guidance for registration applications on the content and qualification of impurities in new drug products produced from chemically synthesised new drug substances not previously registered in a region or member state. Only those impurities in new drug products classified as degradation products of the drug substance or reaction products of the drug substance with an

excipient and / or immediate container closure system are addressed in this guideline.¹²

(C) Impurities: Guideline for Residual Solvents Q3C (R5): The main objective of the Q3B (R2) guideline is to recommend acceptable amounts for residual solvents in pharmaceuticals for the safety of the patient. The purpose of providing acceptable levels of residual solvent is to recommend use of less toxic solvents and to describe levels of residual solvents which are toxicologically acceptable in pharmaceutical products.¹³

(D) Guideline for Elemental Impurities Q3D: The main objective of the Q3D guideline applies to new finished drug products and new drug products containing existing drug substances. The drug products containing purified proteins and polypeptides. This guideline does not apply to herbal products, radiopharmaceuticals, vaccines, cell metabolites, DNA products, allergenic extracts, cells, whole blood, cellular blood components or blood derivatives including plasma and plasma derivatives.¹⁴

United States Food and Drug Administration (USFDA): The U.S. Food and Drug Administration (FDA or USFDA) is an agency of the United States Department of Health and Human Services and is responsible for controlling and supervising the safety of foods, dietary supplements, drugs, vaccines, biological medical products, blood products, medical devices, radiation-emitting devices, veterinary products, and cosmetics.¹⁵

The Guidelines of impurity profiling in USFDA are mentioned below.

(A) Impurities in New Drug Substances Q3A¹⁶

(B) Impurities in New Drug Products Q3B (R2)¹⁷

(C) ANDAs: Impurities in Drug Substances

(D) ANDAs: Impurities in Drug Products

ANDAs: Impurities in Drug Substances: The main objective of the ANDA'S guideline is to provide revised recommendations on what chemistry, manufacturing, and controls (CMC) information to include regarding the reporting, identification, and qualification of impurities in drug substances produced by chemical synthesis when submitting:

- Original abbreviated new drug applications (ANDAs)
- Drug master files (DMFs) including type II DMFs
- ANDA supplements for changes in the synthesis or processing of a drug substance¹⁸

ANDAs: Impurities in Drug Products: The main objective of the ANDA'S guideline is to provide recommendations on what chemistry, manufacturing, and controls (CMC) information sponsors should include regarding the reporting, identification, and qualification of impurities that are classified as degradation products in drug products when submitting:

- Original abbreviated new drug applications (ANDAs)
- ANDA supplements for changes that may affect the quantitative or qualitative degradation product profile¹⁹

Control of impurities in active pharmaceutical ingredients (API): During crystallization, the chemicals from the degradation of drug are entrapped. So API manufacturer should take precaution to produce finer crystals in order to prevent entrapment. Washing should be proper to remove unwanted chemicals including residual solvents. Photo sensitive pharmaceuticals have to be packed in proper way to prevent exposure of light. Production method should be based on stability study. In case of diclofenac sodium injections, the aseptic filtration process was used instead of the autoclave method to yield quality product. Over all pharmacopoeias should be more limit specific, precise and regulatory authorities like ICH and FDA should be strict regarding this matter.²⁰

Applications and Significance of impurity profiling: Impurity profiling have found application in monitoring quality and stability of pharmaceutical compounds, whether produced synthetically, extracted from natural products or produced by recombinant methods. Impurity profiling have helped in detecting and consequent removal of impurities in several drug product including alkaloids, amines, amino acids, analgesics, antibacterials, anticonvulsants, antidepressant, tranquilizers, antineoplastic agents,

local anaesthetics and steroids.^{21, 22} **Table 1** shows impurities and method of analysis of several drugs. Following are the important significance of impurity profiling:

- Helps in identification and quantification of compounds.
- It ensures that the impurities give are within the limits as specific under ICH guidelines.
- Improvement of current analytical methods, the origin of impurities can be determined whether it is synthesis related impurity (Organic/ Inorganic/ Residual solvents), or formulation related impurity (Dosage form/ Method/ Environmental related impurity), or degradation- related impurity, or other impurities (Enantiomeric/ Polymorphic/ Genotoxic impurity).
- Helps in control system for impurities involving processing or manufacturing conditions, packaging and formulation.²³
- In case of synthesis related impurities: an alternative route for the synthesis of the API can be developed or the reagent (residual solvent) concentration is determined.
- In case of formulation related impurities: An excipients which affects the stability of b API is thus not incorporated in the formulation of the API or environmental conditions can be controlled to avoid degradation of the API.
- In case of degradation-related impurities: the potential degradation products can be determined through stress testing and actual degradation products through stability studies.
- In case of other impurities:
 - Polymorphic impurity: The polymorphic form of the API present in the formulation can be qualified. The stability of the polymorphic form in the formulation can be determined.²⁴
 - Enantiomeric impurity: The presence of the correct enantiomer (responsible for therapeutic activity of the API) in the formulation can be verified.^{25, 26}
 - Genotoxic impurity: The source of genotoxic impurity can be determined (starting material/reagents/catalyst) and thus be prevented. The genotoxic impurity can be categorized and its risk can be determined.²⁷

TABLE 1: CURRENT MARKETED FORMULATION WHICH CONTAIN IMPURITY

Drug	Impurity	Method
Amphotericin B	Tetraenes	UV Spectroscopy
Atropine sulphate	Apo atropine	UV Spectroscopy
Cloxacilin	N,N dimethylaniline	Gas Chromatography
Doxirubicine Hydrochloride	Acetone and Ethanol	Gas Chromatography
Dextrose	5-hydroxy methyl fulfural	UV Spectroscopy
Ethambutol Hydrochloride	2-amino butanol	Thin layer Chromatography
Fluorescence sodium	Dimethyl formaamide	Gas Chromatography
Farmyctin sulphate	Neamine	Thin layer Chromatography
Marcptopurine	Hypoxanthine	UV Spectroscopy

Case Study on Identification of impurities: Due to the increasing number of drug cases, as well as the widening globalization of illicit drugs, law enforcement agencies worldwide have adopted the strategy of profiling of drug impurities. Detailed impurity information has been reported on the methamphetamine drugs seized in countries such as the European Commission, Japan, Thailand, Korea, the Philippines and Australia, where methamphetamine abuse is one of the most serious drug issues. The information obtained can be used to establish drug trafficking patterns and distribution networks, and to identify methods used in the manufacture of illicit drugs. Methamphetamine hydrochloride is currently one

of the most widely used illicit drugs in the China. However, in the open literatures there has been little information available on impurity characteristics or profiling of methamphetamine drug seizures in China. A total of 48 methamphetamine hydrochloride samples from eight seizures were analyzed using gas chromatography–mass spectrometry (GC–MS) and a flame ionization detector (GC–FID).

Eight seizures of Methamphetamine hydrochloride from BPSB captured between 2006 and 2007 were analyzed. Typically the seizures were crystals and had a purity of more than 95%. Each of seizures weighed over 400g and belonged to a bag.

The contents of each selected bag (seizure) were divided into six samples. Thus, a total of 48 samples were obtained. 10g were weighed out from each sample and crushed. Fifty milligrams were taken for analysis. The each sample was analyzed three times to determine the variability within each seizure and whether the samples from the same bag (seizure) belong to the same batch.

The present method offers superior separation of impurities in methamphetamine hydrochloride crystals using chromatographic techniques. The 17 peaks selected were characteristic and diagnostic for the classification and comparison of chromatograms. The Euclidean distance of 17 relative peak areas after logarithmic transformation was effective for the evaluation of similarity and/or dissimilarity of impurity profiles.

The preliminary work shows that it is very useful for getting intelligence from methamphetamine impurity profiling. Information about the impurities in methamphetamine allowed identification of the drug synthetic routes.

In the drugs manufactured via the ephedrine route where the marker compounds, the aziridines or naphthalenes, were present distinctively.²⁸

Case study on Quantification of active pharmaceutical ingredient and impurities in sildenafil citrate obtained from the Internet:

Consumers can obtain prescription drugs *via* the Internet without any difficulty and professional oversight. The accessibility of prescription drugs produced outside of the United States, most notably sildenafil citrate (innovator product, Viagra®), has been made much easier by the Internet. Clinicians and policymakers are more concern to product quality and patient safety. The US Food and Drug Administration (FDA) has issued warnings to potential buyers that the safety of drugs purchased from the Internet cannot be guaranteed and may present a health risk to consumers from substandard products.

A study was conducted to determine whether generic sildenafil citrate tablets from international markets obtained *via* the Internet are equivalent to the US innovator product regarding major aspects of pharmaceutical quality: potency, accuracy of labelling, and presence and level of impurities. As

in case a total of 15 sildenafil citrate tablets were taken for pharmaceutical analysis out of which 14 generic samples from international Internet pharmacy websites and one was innovator product. According to US Pharmacopeial guidelines, tablet samples were tested using high performance liquid chromatography for potency of active pharmaceutical ingredient (API) and levels of impurities (impurities A, B, C, and D). Impurity levels were compared with International Conference on Harmonisation (ICH) limits. As outcome of among 15 samples, 4 samples possessed higher impurity B levels than the ICH qualification threshold, 8 samples possessed higher impurity C levels than the ICH qualification threshold, and 4 samples possessed more than 1% impurity quantity of maximum daily dose (MDD). For API, 6 of the samples failed to fall within the 5% assay limit.

Outcomes of study revealed that in that manufacturing standards for sildenafil citrate generic drug products compared with the US innovator product are not equivalent with regards to potency and levels of impurities. They have implications for safety and effectiveness that should be addressed by clinicians to safeguard consumers who choose to purchase sildenafil citrate and foreign-manufactured drugs, *via* the Internet.²⁹

CONCLUSION: Impurity profiling has gained immense significance in pharmaceutical product development. New methods are being explored to identify and establish the levels of impurities in drug products which ultimately help in its quality and safety monitoring. The ICH guidelines provide comprehensive guidelines on impurities and implementing these guidelines help pharmaceutical companies to produce drug products which are free from impurities or in which the toxic impurities are in desired levels.

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