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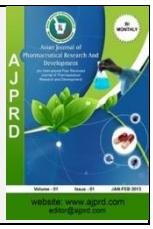

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Review Article

Impurity Profiling: A Review

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A B S T R A C T

Impurities are any substances, such as starting materials or intermediates, that coexist with the parent drug or arise from side reactions. Interest in impurities present in APIs continues to grow. Nowadays, not only purity profile but also impurity profile is mandated by various regulatory agencies. Impurity profiling is a generic name for a group of analytical working groups such as describing, quantifying and characterizing identified and unidentified impurities present in a new drug substance. Impurity profiling is a novel approach aimed at detecting, identifying, structuring and quantifying organic and inorganic impurities and residual solvents in pharmaceuticals. Various regulatory bodies, such as ICH, USFDA, UKMHRA, and India's CDSCO, focus on impurity profiling and have formulated guidelines for impurity management and restriction. Impurities are classified into different categories based on their origin, type of composition, and biological safety. The presence of these unwanted chemicals or substances may affect the safety and effectiveness of the final medicinal product. This review focuses on the sources of impurities, their classification, and various analytical methods for the identification and quantification of impurities. Terms such as residual solvent, by-product, transformation product, decomposition product, reaction product, and related products are often used to define impurities.

Keywords: Impurities, Solvents, Guidelines, Control, Quantification, Existence, Efficacy.

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INTRODUCTION

According to the International Conference on Harmonization (ICH) definition, the impurity profile of a medicinal substance is "a description of the identified and unidentified impurities present in a new medicinal substance" [(7)].

Impurity profiling is the process of evaluating data to establish the biological safety of individual impurities [(2)]. Impurity profiling is performed to maintain the stability or efficiency of the API. Mass production of pharmaceuticals forms the basis of all pharmaceutical industries as it is a source of special quality active pharmaceutical ingredients (APIs)[(11)]. Purity changes over time and is inextricably linked with advances in analytical chemistry [(9)]. There is a growing interest in API impurities. Recently, in accordance with various regulatory requirements, not only the purity profile but also the impurity profile is becoming important [(11)]. In the pharmaceutical sector, impurities are treated as organic substances other than drugs, synthetic ingredients or unwanted chemicals remaining in the API. Impurity profiles have become important due to various regulatory requirements. In the pharmaceutical industry, impurities are defined as organic substances or unwanted chemicals that remain in an active pharmaceutical ingredient (API). Impurities may appear during formulation or during the aging of both API and formulation.

For example, some impurities are named according to the International Conference on Harmonization (ICH).

- By products.
- Perishable products.
- Interactive Products.
- Intermediate.
- Related Products.
- Variants.

Impurity: “Defined as any substance that coexists with the parent drug, such as starting materials, intermediates, side reactions, etc.”

Profiling: This is the identification process to obtain the properties of a substance.

The impurity profile is a description of the identified and unidentified impurities present in a typical batch of APIs produced in a defined controlled manufacturing process. 8 - 10. This is one of the most important areas of activity in the analysis of modern industrial pharmaceuticals. The International Conference on Harmonization (ICH) has issued guidelines on impurities in new drugs, products and residual solvents. Even small amounts of impurities can affect the efficacy and safety of pharmaceuticals. Currently, most drugs used today are of synthetic origin, from which various final formulations are made. These formulations deliver medicinal substances in a stable, non-toxic, and acceptable form that ensures bioavailability and therapeutic activity [(11)].

The regulatory guidelines for impurities in the API

Impurity Monitoring and Control have different meanings. Therefore, simple terminology should be used for questions related to impurities. The US Food and Drug Administration (USFDA) has approved guidelines prepared by the International Conference on Harmonization (ICH). The ICH Guidelines for Impurities have been jointly developed by various regulatory bodies such as the European Union (EU), Japan, and the United States and help ensure consistency in the data requirements that must be submitted to the various regulatory bodies. This guide provides information to sponsors of a new drug application (NDA) or abbreviated new drug application (ANDA) to send with their application, as well as helps FDA reviewers and researchers in a consistent application and interpretation of the rules[(16,18,21)].

The following are various regulatory requirements of ICH Guideline

1. Stability Testing of New Drug Substances and Products.
2. Impurities in New Drug Substances.
3. Impurities in New Drugs.
4. Recommendations Impurities: Residual Solvent.
5. USFDA Guidelines for Impurities in NDAs in New MedicinalSubstances.
6. ANDA Impurities in New Drug Substances.
7. Australian Prescription Drug Regulatory Guide, Treatment Australia (TGA)[(17)].

Sources of Pollutants

Knowledge of pollutants found in commonly used medicines can be easily obtained from current batch analysis and stability studies. Experience in manufacturing certain substances often indicates that not all of the expected impurities are actually present. However, for newly available substances, it is important to be able to estimate the impurities that may be contaminated. Knowledge of the raw materials used, manufacturing methods, and product stability makes it easy to put together a list of possible impurities. For this purpose, impurities that may result from physical contamination or improper storage conditions should be added [(16).]

• Raw materials used in manufacturing.
• Manufacturing process or method.
• Chemical processes and plant materials used in the processes.
• Storage conditions.
• Disassemble[(21)].

We understand that impurities can come from a variety of sources. The most obvious source of impurities is synthesis, during which intermediates and by-products may enter the API as impurities or may be a source of other impurities produced from them. Any impurities that may be present in the starting material can migrate to the active ingredient of interest. In addition, impurities belonging to the inert ingredients (excipients) and solvents used during synthesis must also be considered. Impurities can form at various stages of drug preparation. These impurities may be present in the final drug product. It is also necessary to evaluate the potential reaction products associated with these impurities.

Crystallization Related Impurities

Polymorphism is a term used to describe a system of crystals in which substances can exist in different crystal packings, all of which have the same elemental composition. Crystalline systems in which substances exist in different crystal packings with different elemental compositions are also possible. This phenomenon is called polymorphism. Based on the recognition that the nature of the structure adopted by a given compound upon crystallization can have a significant impact on the solid-state properties of that system, regulatory authorities are calling for the pharmaceutical industry to pay strong attention to polymorphism. The crystal structure properties of a given material can affect the following properties:

1. Electrical conductivity.
2. Crystalline hardness.
3. Crystal shapes and colours.
4. Density.
5. Diffusion.
6. Dissolution rate.
7. Electrolytic conductivity.
8. transition enthalpy.
9. Specific heat.
10. Heat of solution.
11. Hygroscopicity.
12. Latent heat of fusion.
13. Melting or sublimation properties.
14. Phase diagram.
15. Rate of Reaction.
16. Refractive Index.
17. Solubility.
18. surface tension.
19. Viscosity.
20. Volume

Stereochemistry Related Impurities

It is very important to find compounds related to stereochemistry, that is, compounds with similar chemical structures but different spatial orientations. These connections can be thought of as mixings in the API. The simplest case of chirality is seen in molecules with one or more tetrahedral carbon atoms with four different substituents so that the mirror images do not overlap. Chiral molecules can also occur for a variety of other reasons and

should be considered in any impurity assessment. Stereoisomers are possible in molecules that have one of the following properties:

1. One or more centres of chirality.
2. Spiral.
3. flat chirality.
4. Axial Chirality.
5. Torsion Chirality.
6. Phase asymmetry

Chiral molecules are often referred to as enantiomers. Enantiomers are optical isomers that have the same chemical structure but different optical rotations because of their different spatial arrangement. Therefore, unwanted optical isomers are considered chiral API impurities. It is also important to remember that the number of chiral impurities increases with the number of asymmetric carbon atoms in the molecule.

Residual solvent

Water is commonly found in pharmaceuticals. As a result, water is the most common volatile impurity in pharmaceuticals, in most cases, it is not even considered an impurity. It predominates in both medicinal substances and excipients and is also used in formulations. Moisture content can be important when the formulation is packaged so that it is not in equilibrium with the environment. Under these conditions, moisture entering the system through the auxiliary material may be sufficient to cause hydrolysis. Also, water in the environment can affect the drug and very often negatively affect the chemical stability of the drug or the properties of the formulation.[13]

Impurity Classification

(1) According to ICH

Impurities produced in chemical synthesis can be divided into the following categories.

Organic Impurities (Processing and Pharmaceuticals).

Inorganic Impurities

Residual Solvent organic impurities may be generated in drug substances or in the manufacturing process of raw materials. Identified or unidentified, may be volatile or Raw material

- By-product
- Intermediate
- Decomposition.

Impurities generated during the manufacturing process are nothing but inorganic impurities. They are commonly known and identified and include:

•Reagents, Ligands and Catalysts

• Heavy Metals and Other Residual Metals

• Inorganic Salts

• Filter Aids, Other Materials such as Charcoal Residual solvents can be used as diluents to produce solutions and suspensions that can be organic or inorganic liquids. in drug synthesis. non-volatile, and include

(2) Pursuant to USP

Impurities described in the USP may be classified in another section.

- Impurities in official literature/publications.
- Common impurities
- Volatile organic impurities.

Impurities are classified into different categories based on their origin, type of composition, and biological safety.

ICH classified drug impurities into three main categories.

organic impurities, inorganic impurities and residual solvents [14].

Organic Impurities

These impurities may arise during the production and/or storage of medicinal substances (degradants). Impurities associated with the synthetic process may come from the starting materials, intermediates, reagents, ligands and catalysts used in chemical synthesis, as well as by-products of by-products or from excess reactions in chemical synthesis. Degradation impurities are formed in drug substances as a result of degradation of the final product during manufacturing or as a result of chemical degradation or storage under inappropriate or stressful conditions. These may be identified or unidentified, volatile or non-volatile chemicals. During the synthesis of chiral medicinal substances, chiral impurities are formed and transferred to the final medicinal substance. These impurities may have a lower potency compared to the drug substance and must be removed or controlled in the feedstock, intermediate or final stages.

Inorganic Impurities

Since various inorganic raw materials are used to synthesize pharmaceuticals, there is a possibility that metal and non-metallic inorganic impurities may be transferred to pharmaceuticals. These impurities are classified as follows: Raw materials used in the synthesis of medicinal substances such as acids, alkalis, alkaline earth metal compounds, reagents, catalysts and inorganic salts contribute to the formation of inorganic impurities. Metal residues and heavy metal impurities typically arise from water and metal catalysts used in drug synthesis. In addition, these impurities can form as a result of leaching equipment used in the process, such as reactors, micron filters, transfer lines, centrifuges and dryers. Residual metallic impurities are not curable and can be avoided by using distilled water and a glass reactor.

Residual Solvents

Organic volatile chemicals in pharmaceuticals are commonly referred to as residual solvents. They are used or produced in the manufacture of medicinal substances. These solvents are ineffective, in some cases, toxic and must be removed from the drug substance. Although these solvents are not completely removed by actual manufacturing techniques. The use of certain solvents known to cause toxicity in the manufacture of medicinal substances should be avoided. Residual solvents have been assessed for their potential risk to human health and have been assigned one of three ratings based on this.

Solvent class 1

The use of this solvent should be avoided due to known carcinogens that are harmful to humans and the environment. E.g., Benzene, 1,2-dichloroethane, 1,1-dichloroethene and carbon tetrachloride.

Class 2 Solvent

This solvent is limited because it is not genotoxic, but neurotoxicity and teratogenicity are suspected.

Class 3 Solvent

This solvent has a low potential for toxicity to humans with a PDE greater than 50 mg/day. E.g., acetic acid, ethanol and methanol. Solvents for which no appropriate toxicity data have been found should be justified and restricted from the drug substance. E.g., Trifluoroacetic acid, trichloroacetic acid and isooctane according to the permissible daily exposure (PDE)

Genotoxic Impurities

Based on a Toxic Risk Assessment Genotoxic impurities are compounds that can damage DNA at any level of exposure and such damage can cause tumorigenesis. Classification of an impurity as genotoxic means a positive result of an in vitro or in vivo genotoxicity test. Functional groups in the following compounds are known to be involved in DNA reactions that can be used as structural warnings. Structure of warning functional groups of impurities. These genotoxic impurities are further classified into five classes based on risk assessment

Class 1

These impurities have established mutagenic and carcinogenicity data and are known to pose the most serious risks and should be addressed through process changes. If this is not possible, these impurities should be limited to a "Toxic Risk Threshold (TTC)" as a last resort.

Class 2

These impurities have established mutational data, but their potential to cause carcinogens is unknown. Therefore, these impurities must be controlled using the TTC method.

Class 3

These impurities have a warning unrelated to drug structure and unknown genotoxic potential. Based on the functional group of the molecule, it can be associated with a genotoxic substance. The toxicity of these impurities is determined based on the structure activity relationship (SAR).

Class 4

These impurities have a structure similar to that of medicinal substances and additionally contain functional groups or fragments potentially common to the original structure.

Class 5

This impurity has no interfering structure and is not genotoxic according to data. These compounds should be treated as common impurities and managed according to ICH guidelines.

Chiral impurity

An organic impurity present in a drug substance with a druglike structure, but only with a difference in the spatial orientation around the chiral carbon atoms of the molecule. For example, Besifloxacin hydrochloride is a rhizome and its mixture A is an isomer. Medicinal substances with optical isomers contain these types of impurities. These impurities have different therapeutic and pharmacological profiles than drugs and, in some cases, can be toxic. For example, the drug thalidomide has two isomers in one chiral centre, rhizomes are sedatives, and the isomers are teratogenic impurities that cause birth defects. Therefore, it is necessary to control the impurities in these medicinal substances.

Extractable and Leachable Impurities

Extractable Impurities are compounds that can be removed from the coating of elastomeric components, plastic components or containers and closure systems in the presence of a suitable solvent and the leachable material is an elastomeric or plastic component. A compound that leaches from the coating. Container and closure systems resulting from direct contact with the drug. These impurities are commonly found in pharmaceuticals.

Miscellaneous Impurities

The addition of the aforementioned impurities, unwanted foreign matter or particulate matter in filter aids such as glass, ceramics, hydro filters, activated carbon, and textile filters can also contribute to the formation of impurities. Regular monitoring of fibre and black particles of essential drugs is essential to avoid contamination. These impurities can be removed using good manufacturing methods [5].

Impurities come from

Interaction between primary packaging and pharmaceuticals

(1) During contact between processed materials and storage bags, lids, filters, tube materials, etc.

(2) Impurities are also introduced during storage

(3) Impurities in labels and inks Including, packing, etc.

(4) Impurities (called genotoxic impurities) may be present during product synthesis, such as solvents, residues, catalysts, and reaction products of synthesis [15].

Impurity Detection Method

1. Separation and Characterization
2. ColumnChromatography
3. Gas Chromatography
4. Flash Chromatography
5. TLC
6. GC
7. HPLC
8. HPTLC
9. Capillary electrophoresis (CE)[15].

It is very important to confirm the quotation from the sample if possible. If a specific impurity content is estimated to be greater than 0.1%, it should be evaluated according to FDA guidelines. Hyphenated methods, such as mass spectrometry, gas chromatography, liquid

chromatography,various other chromatographic spectral ratios, are ideal for preliminary characterization of impurities.

A. Spectroscopy.

B. Chromatographic methods.

C. Combination of spectroscopic and chromatographic methods. (i.e., hyphenation method)

Very sophisticated instruments such as mass spectrophotometers combined with gas chromatography or high-performance liquid chromatography (HPLC) are expected to be tools to identify trace components in various formulations. Various methods are used to characterize impurities. As follows

(1) NMR (Nuclear Magnetic Resonance).

The ability of NMR (Nuclear Magnetic Resonance) to provide information on specific binding structures and to study the stereochemistry of drugs of interest in formulations becomes an important analytical tool to determine structural properties. The ability to measure NMR-based diffusion coefficients to distinguish between non-numeric and dimeric substances was confirmed using standard mixtures of genuine materials containing both monomers and dimers. Unfortunately, NMR has traditionally been used as a less sensitive method compared to other analytical methods. A typical sample requirement for NMR analysis of pharmaceuticals is 10 mg compared to mass spectrometry, which requires less than 1 mg.

(2) Mass spectroscopy (MS)

Mass spectroscopy has been increasingly influential in pharmaceutical development over the past few decades. Advances in interface design and efficiency directly related to mass spectrometry (MS) separation techniques for monitoring, characterizing, optimizing and quantifying active pharmaceutical compounds present at the heart of pharmaceutical products or drugs have been reaffirmed. When one method is not suitable to provide the required selectivity, an orthogonal combination of chromatographic methods such as HPLC, high performance liquid chromatography (HPLC), and HPLC can be combined with capillary electrophoresis (HPLC) for rich spectroscopy such as HPLC-NMR. Provides analysis information. or HPLC-MS, which can be a unique tool for confirming the quality of finished products [(10)].

1. LCMS

This is an example of a reversed-phase LCMS analysis in which gradient elution using two different soft ionization methods consists of atmospheric pressure ionization using an electrospray source (APIESI) and chemical ionization of allethrin LCMS is similar. Applies to gas chromatography and mass spectrometry (GCMS) as it is more problematic to remove the carrier liquid from the HPLC eluent before the sample enters the MS source. 0.5 - 0.2 ml/min is a typical eluent flow rate that MS pumping systems cannot handle, so some new technologies such as walking belts, suction systems, vacuum nebulizers and jet separators are used to remove the solvent and pass it through. source of the analyte. For example, a study of the ester of 10-alpha-methoxy-16-dimethyl-ergoline-8-methanol with 5bromonicotinic acid (nicergoline) was performed using a mixture of methanol and ammonium acetate as the mobile phase. This material was characterized by LCMS in terms of molecular weight.

2. LCMS-MS

A recently developed method. Due to the mild nature of atmospheric pressure chemical ionization (APCI) and atmospheric pressure ionization (APPI), this system is widely used for complex analysis of mixtures of thermally responsible and biologically important molecules such as domperidone. The LCMS-MS characterization and quantification of the four impurities in the piperazine phosphate material was developed according to the ICH guidelines. This method has been cited and certified by ICH. Another example is the identification and determination of low levels of methyl methane sulfonate and ethyl methane sulfonate present as impurities in emtricitamine.

3. GCMS

This method has become the most suitable and powerful method available to chemists for the complete analysis of complex mixtures. Samples are injected into the GS and spectra are generated by separating them from the GC and stored on the computer for processing. In this case, the GC connects or connects to the MS method through an interface that uses the diffusion coefficient of the carrier gas to increase the sample concentration in the carrier gas. The scanning process is very fast, allowing MS to be obtained by eluting a single peak from the GC block. One of the major problems found was the lack of an efficient gas separator or interface to the GCMS. Examples of GC-MS separation and characterization include profiling of the synthetic pesticide impurity allethrin using atmospheric pressure ionization, electrospray source (APIESI), and GCMS chemical ionization.

4. HPLCDADMS

High performance liquid chromatography with UV diode array detector and mass spectrometer combined. This type of technology is invented and used almost constantly. Now NMR has been added to this combination to provide DADNMRMS HPLC on commercial instruments. This method is used to analyse impurities such as doxycycline, metacycline and 6-epidoxycycline using oxalic acid and acetonitrile as mobile phases. HPLCDADMS are combined to work together to provide complete identification, characterization and measurement of impurities present in active pharmaceutical ingredients.

5. HPLCDADNMRMS

HPLC-DAD-MS/SPE-NMR transfer scattering method was used to identify isomeric isomers of iridoid glycosides as trace constituents of Hapag phylum procumbens plant extracts. Therefore, the use of this method provides the spectral data necessary to describe the structure.

6. Capillary Electrophoresis Mass Spectrometry (CEMS)

CEMS employs a recently developed analytical technique to support impurity profiling of active pharmaceutical ingredients. The capillary electrophoresis method is based

on a different principle of separation technology and has a different approach to selectivity compared to other separation methods. Capillary electrophoresis involves mass spectrometry using various ionization techniques such as ESI, APPI and APCI. The CEMS method can be useful for determining impurities and elucidating the structure of compounds. This method allows the online transfer of analytes from the electrophoretic capillary to the mass spectrometer without compromising separation efficiency. This method separates easily ionized polar compounds from solution. As some variations of publications are observed in CEMS, this method is not widely used in routine work and has some limitations as shown below.

- Limited sample size.
- Analyse without compromising separation efficiency.
- Permeate flow time tends to change with changes in ambient temperature.
- In general, you cannot use non-volatile buffers with this method.

7. Tandem Mass Spectrometry

This is a widely used analysis method. It operates on permanent loss of product ions, precursors and neutral scanning modes, increasing the selectivity of quantitative mass spectrometers. In this method, an inert gas is generated in which collisions occur due to fragmentation or dissociation of selected ions or product. Precursor ions may include selection of ions of interest, activation of those ions, and mass spectrometry of ionic products. This method is suitable for structure determination and biopolymer sequencing[20].

Current Good Manufacturing Practice

Current Good Manufacturing Practice (cGMP) has become our way of life in the healthcare industry. The trend towards paperless technology with cGMP will continue. FDA submissions for new products are usually made electronically. Laboratory management systems for quality control (LMS) will become commonplace with a sharp decline in manual manuscripts. The industry has not yet realized the importance of the FDA's Process Analytical Technology (PAT) initiative. PAT is the clearest future prospect of any published FDA guidance. What the future of QC production and testing will look like is documented in the lines (and in-between) of this guide. At the heart of PAT is the concept of a controlled and controlled production process that is significantly different from a batch production system. Based on linear test results, data processing decisions are made without subjective human intervention (e.g., art gives way to science). Efforts to harmonize rules, regulations, guidelines and pharmacopeia in this ever-shrinking world in this global economy will continue with the frustration that countless other world organizations and state bureaucrats will agree.

Isolation and Identification of Impurities in Active Pharmaceutical Ingredients

The impurity profile is a description of identified and unidentified impurities present in a new drug substance.The impurity profiling process typically begins with impurity detection, followed by isolation and characterization. For all three types of impurities, it is important to develop reliable methods that can be ultimately validated during process development and referenced for QA/QC. The development of reliable methods for very low-controlled impurities, such as genotoxic impurities, adds an additional challenge to this process. The main analytical tools for the analysis of impurities include spectroscopy, chromatography and various combinations of these i.e., tandem methods. The appropriate method is selected according to the nature of the impurity and the level of information required for the analysis. Pharmaceutical development presents a variety of analytical challenges that require more than one analytical method. Methods such as LC/UV, LC/MS, GC/MS, CE/MS, and LC/UV provide orthogonal detection and additional information to solve these problems in minimal time.As a result, they play an important role in profiling pharmaceutical impurities fromidentification to final.

API-related impurities fall into the following categories:

1. Organic impurities
2. Inorganic Impurities
3. Residual Impurities [9]

Organic impurities

Organic impurities may occur during the production and/or storage of medicinal substances. For example, large quantities of paracetamol have limit testing for par aminophenol, which can be a starting material from one manufacturer or an intermediate from another.

Inorganic Impurities

Inorganic impurities can also be generated from the manufacturing process of bulk pharmaceuticals. They are usually impurities are rarely present. some processes can have problems if the manufacturer does not take proper care during manufacturing.process and the reactors that are acidified or acid hydrolysed (if stainless steel reactors are used).

These heavy metal contaminations can be easily avoided with desalinated water and enamel reactors.

Other materials (e.g., filtration aids, activated charcoal, etc.) Filtration aids, such as filters or centrifuge bags, are routinely used in factories that manufacture bulk pharmaceuticals, and activated charcoal is often used as well. increase. Regular control of bulk pharmaceutical fibres and black particles is essential to avoid this contamination.

Organic Volatile Impurities / Residual Solvents Organic Volatile Impurities are residual solvents that may be contained in the drug substance.

Enantiomer Impurity

Theindividual enantiomers of a chiral drug are now considered an improved compound that can provide an increased therapeutic index with a better pharmacological profile and a more favourable side effect profile. However, the pharmacokinetic profiles of levofloxacin (the isomeric form) and ofloxacin (the rhizome form) are similar, indicating that there is no advantage of one isomer in this regard. For manufacturers of single enantiomers (eutomers), unwanted stereoisomers in drug management are treated the same way as other organic impurities.

Impurities related to stereochemistry

Finding compounds related to stereochemistry is very important. That is, compounds with similar chemical structures but different spatial orientations. These connections can be thought of as mixings in the API. The single enantiomeric form of the 17- 18 chiral drug is now considered an improved compound that can provide a better pharmacological profile and increased therapeutic indices. (S-isomeric forms) are similar but different examples include levofloxacin (Ofloxacin), esomeprazole (S-omeprazole), and levalbuterol (R-ibuterol).

Reaction Solvent Impurities

Some solvents that are part of the reaction act as sources of impurities. For example, methylene chloride often used as a solvent for Friedel-Crafts acylation of benzene or phenyl derivatives. Impurities in the solvent can also be a source of pollution. For example, 2-hydroxytetrahydrofuran is an impurity in tetrahydrofuran that is widely used as a solvent for Grignard reagents [(12)].

Factors Affecting Formulation-Related Contamination

1. Unfavourable temperature exposure: Substances that are unstable to heat or tropical temperatures lead to the decomposition of active ingredients and the formation of impurities, heat sensitive and their deterioration has led to loss of efficacy.
2. Exposure to light: Photosensitive materials decompose when exposed to light / UV light to form impurities.
3. Moisture: May be harmful to powders and formulations containing solid dosage forms. Impurity formation during aging. Interactions between the components contained in the formulation cause the interaction, which leads to the formation of impurities, functional group related impurities

- Ester hydrolysis: Pharmaceuticals such as aspirin, benzocaine, cocaine, and ethyl paraben undergo ester hydrolysis.
- Hydrolysis: Drugs such as benzylpenicillin, barbital, and chloramphenicol are usually hydrolysed.
- Oxidative Degradation: Drugs such as hydrocortisone, methotrexate, heterocyclic aromatic rings, nitroso / nitrile derivatives.
- Photolytic disconnection: A product that is exposed to light during storage until it is manufactured, used in a hospital, or used by a consumer.
- Decarboxylation: Some dissolved carboxylic acids, such as para-amino salicylic acid, lose CO_2 when heated [(17)].

Development of analytical methods

Development of new active substances requires meaningful and reliable analytical data in various phases of development.

- Selection of sample set for the development of analytical methods
- Screening of chromatographic conditions and phases. Linear solvent intensity model of gradient elution
- Optimization of methods for fine-tuning robustness and robustness parameters. USP S/N = 2 x Height x UV / Peak-to-Peak Noise Scale How to Determine or Determine Exposure

Limits: Residual Solvent Class

Class A: Solvents to avoid, known human carcinogens

Class B:Restricted solvents, neurotoxins, teratogenicity

Class C: Less likely to be toxic

Option 1: Oral Calculated assuming a concentration of 10 g (ppm) = (1000 µg / mg) x PDE) / dose.

Option 2: Add Residual Solvent According to the ICH guidelines for impurities in new dry products, it is considered unnecessary to identify less than 0.1% of impurities unless the potential impurities are abnormally serious or toxic[(17)].

Regulators involved in impurity profiling

There are various regulatory agencies to identify contaminants in the active ingredients of pharmaceutical products, such as ICH, USFDA, EMA, CDSCO, Canadian Medicines and Health Authority. Such regulators are described below.

ICH

This stands for International Harmony Conference. It is used to register medicines used by humans. ICH is unique in that it connects regulators with the pharmaceutical industry to discuss the scientific and technical aspects of drug approval. ICH's mission is to achieve greater harmonization to ensure that safer, more effective and higher quality medicines are developed and registered in the most efficient way. These activities were carried out to promote public health, avoid unnecessary duplication of human clinical trials, and minimize the use of animal experiments without compromising safety and efficacy. I have divided the guidelines into four categories.

Quality Guidelines: To achieve quality, they are implementing a more flexible approach to pharmaceutical quality based on stability studies, contamination testing-related thresholds, and good manufacturing practices.

Safety Guidelines: ICH has created comprehensive guidelines for achieving safety and reducing potential risks such as carcinogenicity, genotoxicity and reproductive toxicity.

Efficacy Guidelines: For efficacy, relate to clinical trial design, conduct, safety, and reporting. It also contains new types of drugs derived from biotechnology processes. The main goal is to make more targeted drugs. Interdisciplinary Guidelines: Different in quality, safety and effectiveness. It contains ICH medical terminology and general technical documentation.

USFDA

Abbreviation for the United States. Food and Drug Administration. The FDA is primarily responsible for protecting public health by ensuring the safety, efficacy, and safety of human and veterinary drugs, biological products, medical devices, cosmetics, and products that

emit radiation. It is also responsible for regulating the manufacture, marketing and distribution of tobacco products to prevent human health and reduce tobacco use. It plays a major role in the country's counter-terrorism operations. The FDA fulfils its responsibilities by ensuring the safety of food supplies and facilitating the development of medical devices for public health. They regulate foods, including supplements, food additives, and other foods. Regarding drugs, we regulate prescription and non-prescription drugs. For bio pharmacy, we regulate vaccines, blood and blood products. The other regulates medical devices, cosmetics, veterinary products, tobacco products, etc. The USFDA is the oldest comprehensive protection agency in the United States federal government.

FDA organization consists of

• Commissioner's office

• Food and veterinary office

• Global regulatory operations and policies office

• Medical products and tobacco office

• Operations office

EMA

This basically means the European Medicines Agency. It is a decentralized institution of the European Union based in London. It is an institution responsible for the scientific evaluation of drugs developed by pharmaceutical companies. The main responsibility of the European Medicines Agency is the protection and promotion of public and animal health, carried out through the evaluation and supervision of medicinal products for human and veterinary use. The FDA is responsible for the scientific evaluation of applications for European Union registration of medicinal products for human and veterinary use. Much of the scientific evaluation is conducted by its own scientific committees, which include members of the EEA countries and representatives of patient organizations, consumers and healthcare professionals. The Commission carries out various tasks related to the development, evaluation and management of pharmaceuticals in the EU.

EMA is responsible for coordinating drug safety monitoring or pharmacovigilance systems. It monitors drug safety through the EU network and based on information on the balance of benefits and risks of drugs are available and have changed since approval.

- This agency provides special reports on pharmacovigilance activities for centrally approved products.
- Cost of developing guidelines and setting standards.
- Coordinated monitoring of pharmaceutical companies with drug surveillance obligations.
- Inform the public about drug safety and interact with patient representatives and healthcare professionals.

It is also responsible for coordinating inspections such as.

1. Good Manufacturing Practice, (GMP)
2. Good Clinical Practice, (GCP)
3. Good Laboratory Practice, (GLP)
4. Pharmacovigilance, (PHV)

The European Medicines Agency does not control

1. Drug prices.
2. Patents for drugs.
3. Availability of medicines.
4. Medical Devices.
5. Homeopathic remedies.
6. Herbal supplements. § Food additives.
7. Cosmetics.
8. Drug advertising [(11)].

APPLICATIONS

Numerous applications have been found in pharmaceutical development, monitoring the quality, stability and safety of pharmaceutical compounds produced synthetically, derived from natural products or produced by recombinant methods. Applications include alkaloids, amines, amino acids, analgesics, antibacterial agents, anticonvulsants, antidepressants, sedatives, antitumor agents, local anaesthetics, macromolecules, steroids, and more.

CONCLUSION

Impurity profiling is an important aspect with regard to the quality, safety and efficacy of pharmaceuticals. Impurity profiling and reporting is also mandatory in various pharmacopeia. Isolation and characterization of impurities is necessary for the collection and evaluation of data used in the preparation of biosafety data sheets for new drugs. Therefore, this review focuses on the main aspects of pharmaceuticals and impurities in pharmaceuticals. Thus, the introduction of impurity profiling makes it possible to design products in which the expected impurities do not affect the performance of the final product. This article details impurity introduction, ICH guidelines, impurity sources, classification, impurity thresholds, recent techniques used to isolate and characterize impurities, and impurity profiling applications. Profiling of a test substance according to its impurity content provides the maximum possible explanation of the impurities present therein. Establishing guidelines for the level of impurities in medicinal substances and products sets quality standards for manufacturers. A key aspect is that impurity profiling of new chemical targets should be identified. Pharmaceutical analysts with qualification thresholds below 0.1% for high-dose compounds should carefully consider their analytical skills, especially during the development phase.

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