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Review Article

Regulatory aspects of Impurity profiling

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Abstract

Quality, safety and efficacy of pharmaceuticals play an important role in drug therapy. The safety attribute of drug is established by its pharmacological or toxicological profile along with adverse effects caused by impurities in bulk and dosage form. Impurities present in drug often possess undesired pharmacological or toxicological effects which outweighs the benefits of drug therapy. Recently, many impurity cases have been reported for e.g. NDMA (N-nitroso dimethylamine) impurity in drug product Ranitidine. This may be due to inappropriate follow of impurity related regulatory guidelines or critical voids in regulatory control of impurities or may be lack of appropriate analytical technique for impurity detection. Moreover, in June 2007, EMA became aware of contamination of Viracept® tablets. It was detected with presence of ethyl mesylate impurity, a known genotoxic substance in Nelfinavir mesylate (Viracept®). Due to this, the product was recalled from EU market.

An impure drug is devoid of safety, quality and efficacy and can lead to adverse events. So, drugs of required quality standards should reach the market for patient's safety. Therefore it is important and becomes mandatory to submit impurity data related to isolation, identification, qualification and control of impurities to respective regulatory authorities. This article is an attempt to deliver comprehensive understanding related to various attributes and details about impurity profiling in context with regulatory guidelines along with detail description of impurity data submission to regulatory authority for drug substance (API) to get market approval. This article also focus on ICH impurity guidelines ,sources, classification and quality control of impurities.

Keywords: Genotoxic impurity, EMA , ICH , NDMA impurity, Regulatory authorities

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1. Introduction

According to recent regulatory requirements impurity profile in addition to purity profile has become essential in order to monitor safer drug to reach markets with desired therapeutic activity in appropriate stable form without any adverse effects. Existence of impurities even in minute amount or low concentration, may impact the safety and efficacy of pharmaceutical products leading to unstable, non-therapeutic, and deterioration of pharmaceutical products. Due to this reason, various pharmacopoeia like British pharmacopoeia (BP), United state pharmacopoeia (USP) and Indian pharmacopoeia (IP) are gradually adopting limits for permissible levels of impurities existing in drug substance (API)and drug product or formulation. (1,2)

Impurity: Impurity may be defined as any component other than active pharmaceutical ingredient and excipients. It is devoid of desired pharmacological activity. It may be any degradation product or microbial contaminated product. Acc. to ICH impurity can be:

- Potential impurity: An impurity arising theoretically due to manufacture or storage .for e.g. Ketoamide and enamine impurity present in sitagliptin active pharmaceutical ingredient. (3,4)
- Specified impurity: An impurity having specific acceptance criterion limitation notified in new drug substance specification and individually listed in specification table. This type of impurity can be either identified or unidentified. (5) Identified impurity: These impurities are those for which structural characterisation is accomplished. (3,4) Unidentified impurity : These impurities are those for which structural characterisation is not accomplished. It is determined entirely by qualitative analytical properties (e.g. chromatographic retention time). (3,4)
- Unspecified impurity: These impurities are not individually listed in specifications and are without its own specific acceptance criterion. This type of impurity is restricted by general

acceptance criterion, in the new drug substance specifications. (3,4)

- Genotoxic impurity: Genotoxicity is the property of chemical agents that damages the genetic information within a cell causing mutations, which may lead to cancer. These impurities may alter the genetic code of the cell, causing irreversible damaging effect. (6,7)

Impurity profiling: It mainly covers all aspects related to impurity which mainly includes detection, identification/structural characterisation, isolation, quantitative determination, qualification and control of impurities. (2)

2. ICH Impurity Guidelines:

The international council for harmonization of technical requirements for pharmaceutical for human use (ICH) combines regulatory authorities of different countries (European Union, Japan ,U.S.A)and pharmaceutical industries around the globe under one umbrella for the purpose of discussing scientific and technical aspects of pharmaceuticals .It plays major role in developing ICH guidelines and harmonization of regulatory guidelines ,which helps to bypass the unnecessary delay in drug approval process. The main aim of ICH is to assure safe, effective, and higher quality of medicines meeting higher standards. The guidelines published by ICH are generally common for all regulated and semi-regulated countries. Decision related to adoption of ICH impurity guidelines is not mandatory, instead of it, this decision lies with regulatory authority of respective country. Regulatory authority of different countries can refer either ICH impurity guideline or decide to follow their own impurity guidelines. (8)

ICH impurity profiling guidelines are as follows:

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

Registration applicant can get the guidance from ICH Q3A for the purpose of content and qualification of impurities in new drug substance which is produced by chemical synthesis. This guideline is not applicable for new drug substance which has been used during clinical trials. (4,9)This guideline does not implement to the products as shown in figure no.1.

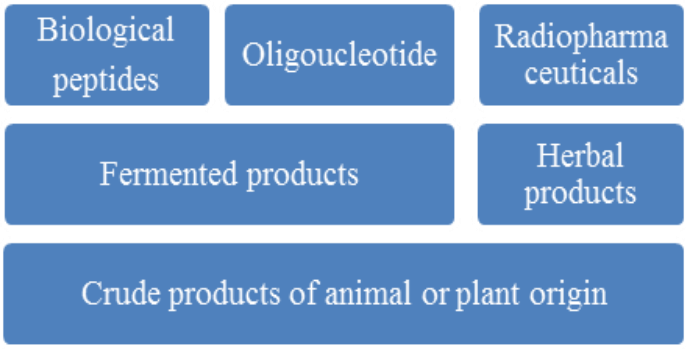

Figure 1. Products not applicable to ICH Q3A

B. Impurities in New Drug Products.

Registration applicant can get the guidance from ICH Q3B for the purpose of content and qualification of impurities in new drug products which are synthesized chemically from new drug substance that should not previously registered in a region or member state. The impurities present in new drug products which are only degradation products or reaction products of the API (Drug substance) are only covered under this guideline. (9)

This guideline not to be implemented for following:

1. Impurities which arises from excipients.

2. Impurities leached from container closure system.

3. New drug product used during clinical trials.

4. Biological/ Biotechnological products, peptides, oligonucleotide, radiophamaceuticals, fermentation products, herbal products, crude products of animal or plant origin.

C. Impurities: Guidelines for Residual Solvents

The ICH Q3C guideline for residual solvents suggests the amount of residual solvents in pharmaceuticals that are acceptable in terms of safety of the patient. The main aim of this guideline is recommendation of less toxic solvents usage in pharmaceuticals and to set acceptable limits of such solvents .This guideline also explain toxicologically acceptable levels for some residual solvents. (10)

D. Guidelines for Elemental Impurities

The quality guideline Q3D is published for the purpose of controlling elemental impurity in medicinal products (new drug products) and establishing permitted daily exposure (PDE) limits for 24 elemental impurities (EIs) for drug products which are administered through parenteral, oral and inhalation routes of administration.

This guideline is applicable to new drug products containing existing API, drug products containing purified proteins and polypeptides, drug products which contain synthetically produced polynucleotides,

polypeptides and oligosaccharides. This guideline is not applicable to: radiopharmaceuticals, vaccines, DNA products, herbal products, gene therapy products, allergenic extracts, cell metabolites, blood products and blood derivatives. (11)

3. Regulatory Impurity Guidelines

Regulatory authorities of various countries like U.S. FDA, TGA, EMA has published several regulatory guidelines related to impurities found in pharmaceuticals. Their main aim was to control impurities at acceptable levels and to possibly remove impurities at most higher level with zero or minimum presence. All the regulatory authorities has contributed their efforts and published guidelines for manufacturer and guidance for pharmaceutical industry with a main goal to provide higher quality standard, higher efficacious and safer medicine around the world. Many regulatory authorities also focused on critical issue related to impurities i.e. genotoxic and carcinogenic impurities. However, ICH has published several impurity guidelines that are harmonised and has global acceptance (accepted mostly by many countries). (2,12–14) Various regulatory guidelines in context to impurities are shown in table no.1.

Table 1. Regulatory Guidelines on Impurity

Regulatory Impurity Guidelines	
Regulatory Authority	**Title of the guideline**
ICHQ1A	Stability testing of new drug substance and products
ICHQ3A(R2)	Impurities in New Drug Substances
ICHQ3B(R2)	Impurities in New Drug Products
ICHQ3C(R6)	Guideline for Residual Solvents
ICHQ3D(R1)	Guideline for Elemental Impurities
ICHM7(R1)	Assessment and control of DNA Reactive (Mutagenic) impurities to limit potential carcinogenic risk.
ICH S2(R1)	Genotoxicity Testing and Data Interpretation for Pharmaceuticals Intended for Human Use
US-FDA	NDAs-Impurities in New Drug Substance
US-FDA	ANDAs-Impurities in New Drug Substances.
TGA	Australian regulatory guideline for prescription medicines.
EMA	EMA Guideline on Genotoxicity Assessment of Herbal Substances

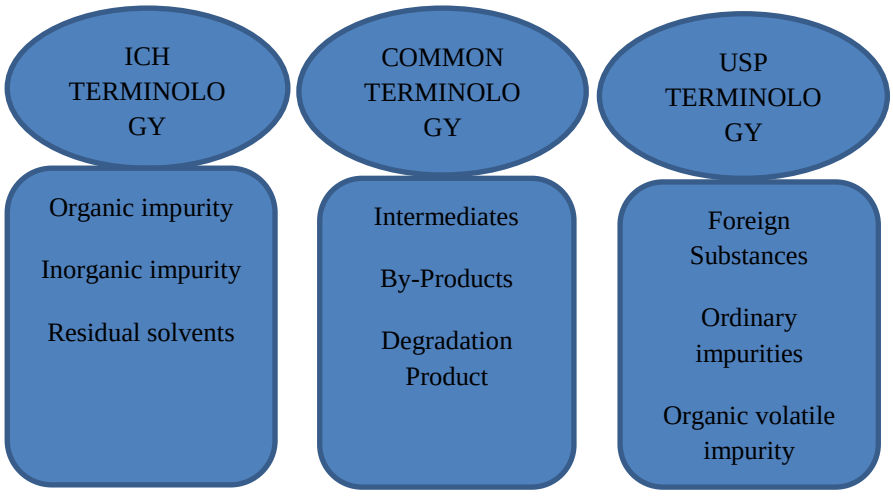

Figure 2. Impurity as per different terminology

4. Classification of Impurities

A. Classification of Impurities as per different terminology is shown in figure no.2. (9,15)

B. ICH Classification of Impurities:

i. Organic impurities: Organic impurities can originate from chemical/manufacturing process or due to storage of API. The nature of these impurities can be volatile or non- volatile, it can be identified or unidentified .The most common examples of such impurities are starting materials, by-products, intermediates, degradation products. (2,15–17) For e.g. p-aminophenol limit test in paracetamol bulk, it can be starting material for one manufacturer or can be intermediate product for other manufacturer. (1)

ii. Inorganic impurities: Inorganic impurities can originate from bulk drug manufacturing process. They are generally of non-volatile nature and are identified impurities. It includes reagents, ligands, catalysts, heavy metals, inorganic salts, other materials like filter aids, charcoal. (14,16,17)

iii. Residual Solvents: These are organic or inorganic liquids which are used as vehicles for the purpose of solution preparation in pharmaceuticals. It can originate from solvents used during chemical reaction, crystallization and purification steps. It includes Benzene, carbon tetrachloride, acetonitrile, chloroform, methanol, acetone, ethanol. (16,17)

C. Classification of Genotoxic impurities

Genotoxic impurities are classified into five categories:

Class 1: Impurities known to be genotoxic (mutagenic) and carcinogenic: This class consists of known animal carcinogens including authentic and reliable data for genotoxic mechanism as well as human carcinogens. The nature of impurity being genotoxic is demonstrated with the help of confirm chemical structure published in scientific literature.

Class 2: Impurities known to be genotoxic (mutagenic), but have unknown carcinogenic potential. This class consists of impurities with evident mutagenicity supported by testing of impurity on basis of conventional genotoxicity tests.

Class 3: Impurities having alerting structure with no relation to API's structure and of unknown genotoxic (mutagenic) potential .This class consists of impurities having functional moieties for which structure is used to link genotoxicity. Although, these moieties are not being tested in isolated form but recognised on the basis of chemistry and utilize knowledge based expert system for structure activity relationship (SAR).

Class 4 : This class consists of impurities having alerting structure correlated (allied) with API .This also includes impurities containing alerting functional group moiety shared and linked with that of API's structure.

Class 5: This class consists of impurities without alerting structure or indication of genotoxic potential. (18-23)

D. Classification of Residual Solvents Impurity

World health organization (WHO) and other global health authorities used "acceptable daily intake" (ADI) in order to describe toxic chemical limit exposures and levels, while the term "tolerable daily intake" (TDI) is used by International program on chemical safety (IPCS).But now a new term "permitted daily exposure"(PDE) described as pharmaceutically acceptable intake of residual solvents in order to avoid ADI'S differing value confusion for same substance is used in current guidelines. Residual solvents are classified as shown in table no.2. (2,10,15,16)

Table 2. Classification of Residual Solvents

Solvent Class	Consideration	Criteria for Consideration	Examples
I	To be avoided	Human carcinogen, toxic and environmental hazard	Benzene, Carbon tetrachloride
II	To be limited	Non-genotoxic animal carcinogen, other irreversible toxicity such as neurotoxicity or teratogenicity	Acetonitrile ,Chloroform, Chlorobenzene
III	Low toxic potential	No health based exposure limit is needed .These have PDEs of 50 mg or more per day.	Acetic acid, Acetone, Anisole

E. Classification of Elemental Impurities

Elemental impurities are classified on the basis of their toxicity (PDE) and likelihood of occurrence in the drug product. The likelihood of occurrence is obtained from factors like: observed natural abundance, probability of use in pharmaceutical processes, possibility of being a co-isolated impurity with other elemental impurities in the materials used in pharmaceutical processes and element's environmental distribution. The elemental impurities are classified into following three classes:

Class 1: This class consists of elements with limited or no use in pharmaceutical manufacturing process. It includes human toxic elements like As, Cd, Hg and Pb. This class elements (As, Cd, Hg, Pb) need to be evaluated during the risk assessment, covering all the potential sources of elemental impurities and routes of administration due to their distinctive nature.

Class 2: This class consists of route-dependent human toxicants. On the basis of relative likelihood (probability) of occurrence of elements in the drug product class 2 elements are further categorised into sub-classes 2A and 2B.

Class 2A: This class elements need to be assess during all potential sources of elemental impurities including routes of administration due to their relatively higher probability to occur in the drug product. Example: Co, Ni , and V

Class 2B: This class elements have reduced likelihood to occur in the drug product associated with its low abundance and their lower possibility to be co-isolated with other materials. Therefore, these elements may be precluded from risk assessment unless these elements are intentionally incorporated during manufacturing of drug substances, and added as excipients or any other components of the drug product. Example: Ag, Au, Ir, Pd, Rh, Ru, Pt, Se.

Class 3: This class consists of elements that have relatively lower toxicity via oral route (high PDEs, generally above 500µg /day) but these elements need to be considering in risk assessment for parenteral routes and inhalation route. In case of oral administration route, if these elements are not intentionally added, they do not required to be consider during risk assessment. In case of inhalation and parenteral routes of administration, evaluation during risk assessment will determine the

possibility for inclusion of class 3 elemental impurities, unless the route specific PDE is greater than 500 µg/day. Ex: Ba, Cr, Cu, Li, Mo, Sb and Sn.

Other Elements: This includes elements with low inherent toxicity, due to which PDEs for these elements are not established. In case this class elemental impurities are present or included in drug product, they are regulated and governed by regional regulations and practices that are applicable for particular elements(e.g.: Mn and Zn considered for patients with compromised hepatic function, Al for compromised renal function),or quality related considerations (e.g. presence of W in therapeutic proteins) for final drug product. Example: Al, B, Ca, Fe, K, Mn, Mg, Na , W and Zn. (11)

5. Sources of Impurities

a. Degradation-related Impurities: The API present in the drug substance may undergo degradation due to presence of moisture, unwanted high temperature, humidity, microbial attack and improper storage leading to pharmacologically inactive drug product. For e.g. The formulation containing combination of nicotinamide, pyridoxine ,riboflavin and thiamine, the presence of nicotinamide results in degradation of thiamine on storage of 1-year shelf life of injection of vit-B Complex. So it is essential in order to maintain safety ,efficacy and quality of drug product to follow stability protocols and follow regulatory stability guidelines (ICH: Q1A-Stability testing of new drug substances and products).It also involves conduction of long term stability testing ,accelerated stability testing and stress testing. (24)

b. Environmental-related Impurities: Pharmaceutical preparations are stable only under proper conditions of temperature, humidity, moisture and light. Exposure to improper and adverse environmental condition leads to pharmaceutically inactive drug product. (24)

- Exposures to adverse temperature: For e.g.: Heat sensitive nature of vitamins as drug substance. Exposure of u.v light to vitamin products results in loss of potency, mostly in liquid formulations. (2)
- Humidity: Humidity exposure to aspirin and other hygroscopic products like ranitidine leads to formation of degradation product with loss of pharmacological activity. (12,25)
- Light-especially UV light: Ergometrine as well as methyl ergometrine is not stable under heat and light. Exposure of heat and light to such substances would result in loss of activity. (25)

c. Crystallization-related Impurities: Existence of a substance in more than one crystalline form (polymorphs) with same elemental composition is called polymorphism. Solvatomorphism refers to existence of substance in different crystal forms having different elemental composition .Therefore after crystallization solid state properties of a system can be affected significantly, thus, regulatory authorities of different countries mandate interest of pharmaceutical companies in polymorphism and Solvatomorphism. (15,26)

Nature of crystal structure affects several properties like: hygroscopicity, conductivity, heat of solution, latent heat of fusion, density, sublimation, dissolution rate, refractive index, surface tension, density, diffusion rate, electrolytic conductivity. Thus pharmaceutical industry should aim at producing drug substance which is devoid of phase inversion and original state of the bulk substance remains intact during whole storage time period. Moreover, formulation of drug substance should be carried in a manner that its phase -purity is intact during manufacturing and storage of drug products. So one of the most important approaches for achieving this can be done by development and validation of assay method for determination of phase composition. (26)

6. Stereochemistry-related Impurity

Compounds having chemical structure similarity but differing only in spacial arrangements of their atoms are called stereoisomers. Carbon having four substituents of different groups and that are non-mirror superimposable are called chiral molecules. Thus it is essential to evaluate chiral molecules .Following molecules shows this phenomenon:

a. Planar chirality (Polycyclophanes)

b. Axial chirality (Spiranes with cyclic skeleton)

c. Topological symmetry (Catenanes)

d. One or more centre of chirality e. Helicity (helical nature of complex protein) f. Torsional chirality (like cis or trans isomers, Rotomers)

Enantiomers are chiral molecules which are optically active having similarity in chemical formula but differing in spatial arrangement of atoms. So there is difference in optical isomers giving rise to d-isomer and l-isomer. The pharmacological and toxicological activity of d-isomer and l-isomer are different in terms of potency and efficacy .Hence optical isomer which is undesired is tagged as chiral impurity of the API. In 1987, FDA has published guidelines to underline this issue directly on drug substance manufacture. (15,26) .In many drugs only single enantiomer is active and thus inactive enantiomer is considered as an impurity. For e.g. The Dextro form of Pilocarpine is only active and levo form is considered as an impurity. (24)

7. Formulation-related Impurities

Impurity can also arise during formulation of drug products due to undesired exposure of heat, light and pH change. During formulation variety of conditions are subjected to API leading to deleterious reaction and degradation.

Formulation related impurity is categorized as:

A. Method related:

Method which is not suitable and sensitive to drug substance (API) can result in pharmacologically inactive and toxic drug product considered as impure. For e.g.: During Sterilization, autoclaving of Diclofenac sodium, well known impurity 1-(2,6dichlorophenyl)-indolin-2-one is formed. (2,25) Due to autoclaving the intra molecular cyclic reaction is generated in diclofenac

sodium resulting in formation of indolinone derivative and sodium hydroxide. The impurity concentration in resultant product in ampoule is found to be exceeding the raw material limits in the BP (British pharmacopoeia). (5)

B. Functional group related impurities:

i. Hydrolysis

Drugs which contain ester as functional group may undergo hydrolysis called ester hydrolysis. Examples: benzocaine, benzylpenicillin, barbitol, chloramphenicol, chlordiazepoxide, lincomycin, cefoxime and oxazepam. (14,15)

ii. Oxidative degradation:

Some drugs are prone to oxidation which results in degradation of the formulation. For e.g.: Hydrocortisone, methotrexate, nitroso and nitrite derivatives, aldehydes (e.g. flavones) phenol derivatives such as catecholamines and morphine. (1,14,15)

iii. Photolytic cleavage:

In some compounds free radical chain reaction is generated due to photochemical energy or when exposed to high energy u.v light. This leads to drug degradation. Hence it is important to formulate and store such substances away from light source. For e.g.: Fluoroquinolones antibiotics are susceptible to photolytic cleavage. (1) In eye drop of ciprofloxacin, photolytic cleavage induced by sunlight results in formation of ethylenediamine analog of ciprofloxacin. (27) Ergometrine, riboflavin, nifedipine, and phenothiazines are susceptible to photo-oxidation. (1)

iv. Decarboxylation:

The phenomenon of loss of carbon dioxide from carboxyl functional group can lead to formation of impure drug products. For example: p -Amino salicylic acid, Decarboxylation in photoreaction of Rufloxacin. (1)

8. Impurity data Submission for drug substance

As per Regulatory guidelines for drug substance ICHQ3A, applicant need to submit following data related to impurity to their perspective regulatory authority (4):

(i). Rationale for reporting and control of impurities:

A. For Organic Impurities:

The Registration applicant should summarize following:

- Data of actual and potential impurity arising during: Synthesis, Purification, Storage
- Laboratory study data for impurity detection.
- Impurity structural characterisation studies.
- Include test results of: a. Development process batches. b. Proposed commercial batches. c. Stress testing storage batches.
- If identification of an impurity is not feasible, in that case, summary of the laboratory studies demonstrating unsuccessful effort to be submitted in the application.

B. Inorganic Impurities:

- Detection and quantification of inorganic impurity should be mandate according to pharmacopoeial procedures.
- Criteria to include/exclude inorganic impurity in new drug substance should be clearly and briefly discussed in Specifications.
- Acceptance criteria mandatory to be based on the prescribed Pharmacopeial standards or known safety data.

(ii). Analytical procedures:

- Applicant should document the evidence demonstrating analytical procedures are validated & suitable for impurity detection and quantification.
- Registration applicant should discuss differences in analytical procedures used during developmental batch product and proposed commercial batch product.
- The comparison result of analytical response for impurity with appropriate reference standard for measuring level of organic impurity to be discussed in the application.
- The reference standard should be evaluated and characterized according to their intended use.
- Estimation of identified and unidentified impurity on the basis of accepted criteria and analytical procedure to be discussed in registration application.

(iii). Reporting impurity content of the batches:

a) Analytical results of all batches of clinical safety and stability testing for new drug substance should be documented in an application

b) There should be numerically representation of the quantitative result of the impurity.

c) Representative chromatograms (from representative batches of analytical validation studies) showing separation and detectability of impurities should be included in the application.

d) Results need to be reported and documented in a prescribed format as shown in figure no.3.

e) Report of each new drug substance batch should include:

- Batch identity and size
- Date of manufacture
- Site of manufacture
- Manufacturing process
- Use of batches
- Impurity content ,individual and total
- Reference to analytical procedure used

(iv). Specification:

Specification refers to list of tests (qualitative and quantitative tests) and references to analytical procedures with appropriate acceptance criteria .These are generally numerical limits, ranges or other criteria with reference to specific test described.

List of impurities should be included in the specification of new drug substance. Selection criteria for impurities inclusion in new drug substance specification should be based on impurity detected in batch of proposed commercial process. There should be documentation of rationale used for including or excluding of impurities in specification. In case of unidentified impurities, the assumption made and procedure used for impurity level establishment should be clearly mentioned in the document. An appropriate qualitative analytical descriptive label (e.g.: "unidentified A", "unidentified with relative retention of 0.9") should be used to refer specified unidentified impurities. For unspecified impurity a general acceptance criterion of less than (<) the identification threshold should be included and for total impurities there should be inclusion of acceptance criterion.

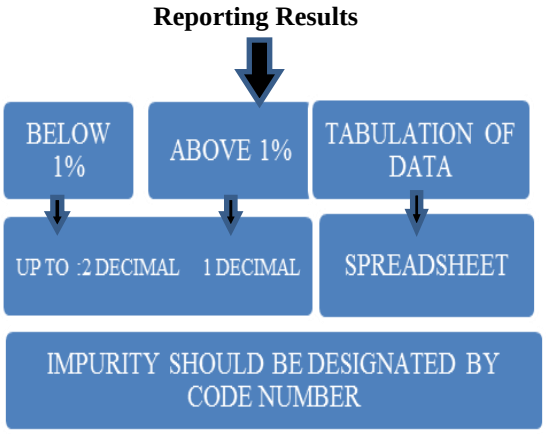

Figure 3. Reporting results for impurities

The level for setting acceptance criterion should be justified by safety data and should not be higher than this level. The level should be in consistent with that of achievable manufacturing process and analytical capability.

In summary section, specification of new drug substance should include, following list of impurities:

a. Organic impurities: This should include each specified identified impurity, each specified unidentified impurity, total impurities and any unspecified impurity having acceptance criterion of less than (<) identification threshold.

b. Inorganic impurities

c. Residual solvent impurities.

Conformance to specifications: It means if we test drug substance according to the listed analytical procedures, it will satisfy and meet all the listed acceptance criteria. Specifications are meant to be critical quality standards that are generally proposed and justified by the manufacturer; these are approved by regulatory authorities as a condition for the purpose of approval.

(v).Qualification of impurities:

Qualification is basically a process to acquire and procure as well as evaluating the data in order to establish biological safety of an individual impurity or a given impurity profile at specified level. It is a significant process if there is a previous evidence of adverse reaction in patients (patients adverse event history) correlated with impurity present in certain drugs or therapeutic classes.

Consideration for impurity qualification

Qualification threshold: It is basically a limit serving a deciding factor whether to qualify an impurity or not. If the impurity level is greater than this threshold then it should be mandatory qualified with help of specific tests and procedures prescribed for impurity qualification.

In cases, if the impurity level is decreased to less than the threshold, then qualification of impurity is not essential. Moreover, availability of scientific literature to qualify an impurity could be considered .If this attributes are not satisfied, then additional safety testing need to be considered. The studies suitable for qualification of impurity (For impurity qualification) depends on several factors like daily dose ,patient population ,route and duration of drug administration .Such studies can be performed sometimes using isolated impurities or usually with new drug substance containing the impurity to be qualified.

The safety evaluation study for qualification of impurity should include the rationale of comparing new drug substance having representative amount of new impurity with already qualified impurity. Safety assessment studies can be performed using samples of isolated impurity. (2,16)

Impurity is considered as qualified impurity when it satisfies following conditions:

- When the scientific literature adequately provide justification of observed level and proposed acceptance criterion for the impurity.
- When drug substance has impurity as its significant metabolite. (12)

- When there is adequate clinical and safety testing of any impurity level present in new drug substance. (12)

9. Quality control of impurities

A. For Drug Substance (API)

According to ICH Q3A, MDD (maximum daily dose) plays vital role in reporting, identification and qualification of impurities. It is important to report and document an impurity if it is greater than (>) reporting threshold. As per the guidelines, it is mandatory to identify the impurity if it is greater than (>) identification threshold. Qualification of impurity is essential as per regulatory guidelines if the impurity exceeds the qualification threshold. (4, 27) The thresholds for drug substance are given in table no.3.

Table 3. Thresholds for drug substances

Maximum Daily Dose	Reporting Threshold	Identification Threshold	Qualification Threshold
≤2g/day	0.05%	0.10% or 1.0 mg per day intake (whichever is lower)	0.15% 0r 1.0 mg per day intake (whichever is lower)
≥2g/day	0.03%	0.05%	0.05%

B. For Drug product *(27)*

According to ICH Q3B, TDI (Total daily intake) plays vital role in reporting, identification and qualification of impurities .The degradation products in new drug products to be mandatory reported if it exceeds reporting threshold. All the degradation products to be identified if it is greater than identification threshold. If the degradation product exceeds the qualification threshold, it is to be mandatory qualified as per the regulatory guidelines. The thresholds for drug product are given in table no.4.

Table 4. Thresholds for drug products

Maximum Daily Dose (1)	**Thresholds** (2,3)
	Reporting Thresholds
≤1g	0.1%
> 1 g	0.05%
	Identification Thresholds
< 1 mg	1.0% or 5 µg TDI, whichever is lower
1 mg - 10 mg	0.5% or 20 µg TDI, whichever is lower
>10 mg - 2 g	0.2% or 2 mg TDI, whichever is lower
> 2 g	0.10%
	Qualification Thresholds
< 10 mg	1.0% or 50 µg TDI, whichever is lower
10 mg - 100 mg	0.5% or 200 µg TDI, whichever is lower
>100 mg - 2 g	0.2% or 3 mg TDI, whichever is lower
> 2 g	0.15%

Notes on Table 4:

(1) It refers to amount of drug substance which is administered on per day basis.

(2) Thresholds in context of degradation products are expressed either in the form of percentage of the drug substance or as total daily intake (TDI) of the degradation product. Lower thresholds are usually appropriate if the degradation product is unusually toxic.

(3) Higher thresholds need to be scientifically justified.

10. Cases of drug impurity

Many drugs have been recalled from the market due to detection of impurities. Drug recalls are the steps or actions which are taken by a firm in order to eradicate a defective, dangerous, impure, harmful and contaminated drug product from the market. It can be voluntary initiated by the company as its own decision to remove its own product from the market or it may be requested by particular drug regulatory authority of the country. For ex: FDA in U.S.A. (28-30)

Drug regulatory authorities of different countries become aware of NDMA impurity present in valsartan in July 2018.Valsartan is a medicine used in cardiovascular diseases belonging to a category of angiotensin II receptor blocker. Nitrosamines are carcinogenic impurity and can probably cause cancer to humans. It can occur during synthesis of API or it can be process related impurity. Presence of nitrosamines in medicine is unacceptable. However a specified acceptable limit for particular impurity is generally specified by regulatory authorities.

Moreover, in addition to NDMA impurity, other nitrosamine impurity like NDEA, NDIPA, NEIPA and NMBA were also detected in family of sartans. More recently, impurities related to nitrosamine have been also reported in Ranitidine as well as pioglitazone containing product. (30-35)

(a) Findings w.r.t Tetrazole ring in Sartans in U.S market.

It is concluded that in most of the cases Sartans which contain tetrazole ring in their chemical structure like

valsartan, losartan, olmesartran, irbesartan were found to be carcinogenic due to presence of nitrosamine impurity. These products were recalled and removed from the market because they possess risk to patients safety and health. It also affects overall quality of the drug. It was noticed that the drug candesartan also contains tetrazole ring but the lots were not removed from the market. However, the sartans which do not have tetrazole ring in their chemical structure like telmisartan were not removed from the market. (32, 36)

(b) History of product recall by different companies in past years w.r.t NDMA, NDEA, NMBA impurities in sartans.

In the year 2018 companies like Torrent, Camber, Teva, there was a recall of valsartans due to NDMA impurity. Mylan, Teva also had a recall of valsartan due to NDEA impurity. Aurbindo pharma recalled irbesartan in 2018 and valsartan in 2019 due to NDEA impurity. Losartan was recalled by camber in 2019 due to NMBA impurity. Aurbindo pharma recalled valsartan in 2019 due to NDEA impurity.

On 15/4/2020, Amneal pharmaceuticals recalled Nizatidine oral solution 15mg/mL from U.S market due to detection of NDMA impurity. Amneal pharmaceuticals also recalled Metformin hydrochloride extended release tablets, USP 500mg and 750mg due to detection of NDMA impurity. On 05/06/2020 Teva pharmaceuticals recalled Metformin hydrochloride extended release tablets, USP 500mg and 750mg and Apotex Corp. recalled Metformin hydrochloride extended release tablets, USP 500 mg due to detection of NDMA impurity. On 28/2/2019 Camber pharmaceuticals Inc, has announced national wide voluntary recalls of 87 lots of losartan potassium tablets, USP 25mg, 50 mg and 100 mg due to recognition of NMBA impurity. On April, 2020 U.S.FDA announced market withdrawal of all prescription and OTC ranitidine (zantac) drug from the market immediately. This was due to the fact that agency has investigated detection of NDMA impurity in ranitidine medication. (33,34)

11 Conclusion

Presence of impurities in pharmaceuticals has negative impact on whole lifecycle of the drug starting from development stage to the marketing. It impacts the quality, safety and efficacy of drugs leading to undesired pharmacological and non-therapeutic effect. It may also give rise to severe adverse events affecting patient's health. Impurities not controlled under specified safety levels also leads to delay in drug approval process affecting the sale, marketing and overall cost of the drug. Hence uncontrolled impurity has blunder effect on both pharmaceutical industries and patients. So it is important to control impurity under specified safer level. For this, the guidelines are laid down by different regulatory authorities for identification, reporting, isolation, qualification and control of impurities. Implementation of these guidelines serves as a guidance document for pharmaceutical companies and helps them to develop drugs devoid of impurities and in which impurity is under controlled safety levels.

The mandatory requirement of documenting impurity profile data instructed by regulatory authorities for approval process has strengthened the availability of safer drugs to reach markets. The ICH comprehensive and harmonised impurity guidelines and its global acceptance by different regulatory authorities help to fasten the approval process and eradicate unnecessary delay. However there is still need of stringent regulatory framework so that impurity detected post approval of the drugs can be prevented. More stringent pathway will help to reduce post approval adverse event in the population and will reduce the undesired health issue due to impure drug.

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Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this article.

List of abbreviations

ADI: Acceptable daily intake
ANDA : Abbreviated new drug application
API: Active pharmaceutical ingredient
BP : British pharmacopoeia
EI : Elemental impurities
EMA : European medicine agency
EU : European union
FDA: Food and drug administration
ICH : International conference on harmonization
IP : Indian pharmacopoeia
IPCS: International program on chemical safety
MDD: Maximum daily dose
NDA : New drug application
NDEA : N-nitroso diethyl amine
NDIPA:N-nitroso di iso propyl amine
NEIPA: N-nitrosoethyl iso propylamine
NDMA : N-nitroso di methyl amine
NMBA: N-nitroso-N-methyl-1,4-aminobutyricacid
OTC: Over the counter
PDE: Permitted daily exposure
SAR: Structure activity relationship
TGA: Therapeutic good administration
TDI : Total daily intake
USP: United states pharmacopoeia
WHO: World health organization

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