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## IMPURITY PROFILING: A NECESSITY IN THE PHARMACEUTICAL INDUSTRY: AN OVERVIEW

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### Abstract

Impurities in pharmaceuticals are the unwanted chemicals that remain with the active pharmaceutical ingredient (API) or develop during formulation or upon aging of both the API and its formulation. Their presence can adversely affect the safety and efficacy of the pharmaceutical products. In recent times, not only the purity profile but also the impurity profile (i.e., the identity as well as the quantity of impurity in the pharmaceuticals) has become essential as per various regulatory requirements. Impurity profiling is very important during the synthesis and manufacturing of the API and its dosage form, since it helps in providing crucial data regarding the safety limit of several organic and inorganic impurities as well as residual solvents, limit of detection and limit of quantitation. It has numerous applications in the areas of drug design as well as in monitoring quality, stability and safety of pharmaceutical products.

**Keywords:** Impurity profiling, Efficacy, Safety Limit, Drug Design, Quality.

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## INTRODUCTION

In the present era, there has been an ever increasing interest in impurity profiling in the pharmaceutical industry [1]. 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 [2]. 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 [3]. ICH has published guidelines on the impurities in new drug substances [4], new drug products [5], residual solvents [6] and elemental impurities [7].

## IMPURITY

As per ICH Q6A Specifications, it is defined as:

A component of the new drug substance other than the chemical entity defined as the new drug substance.

A component of the drug product other than the chemical entity defined as the drug substance or an excipient present in the drug product [8].

## IMPURITY PROFILING

It refers to all the analytical activities which aim to detect, identify (i.e structural elucidation) and quantify all the types of impurities that may be present in the bulk drug and finished products [9].

## CLASSIFICATION OF IMPURITIES

Impurities can be classified as per different terminologies:

Table No.1: Classification of impurities as per different terminologies [4,10]

DIFFERENT TERMINOLOGIES	TYPE OF IMPURITIES
COMMON TERMINOLOGY	Intermediates, Byproducts, Interaction product, Degradation product, Related product
USP TERMINOLOGY	Foreign substances, Ordinary impurities, Residual solvents
ICH TERMINOLOGY	Organic impurities, Inorganic impurities, Residual solvents

## SOURCES OF IMPURITIES [11,12]

### SYNTHESIS RELATED IMPURITIES

These impurities are a common source of impurities in new drug substances during its synthesis and mainly arise from raw materials, solvents, intermediates or by products. They are further categorized as:

#### 1. ORGANIC IMPURITIES:

**1.1 Starting materials or Intermediates:** It is a common source of impurity especially in new drug substances. Even though the desired end product is always washed with a solvent, the residual unreacted starting material may still be present.

Example:

A potential impurity identified, in the synthesis of Baclofen (Muscle relaxant), was p-chlorophenylglutaric acid, which is an intermediate obtained during its synthesis [11].

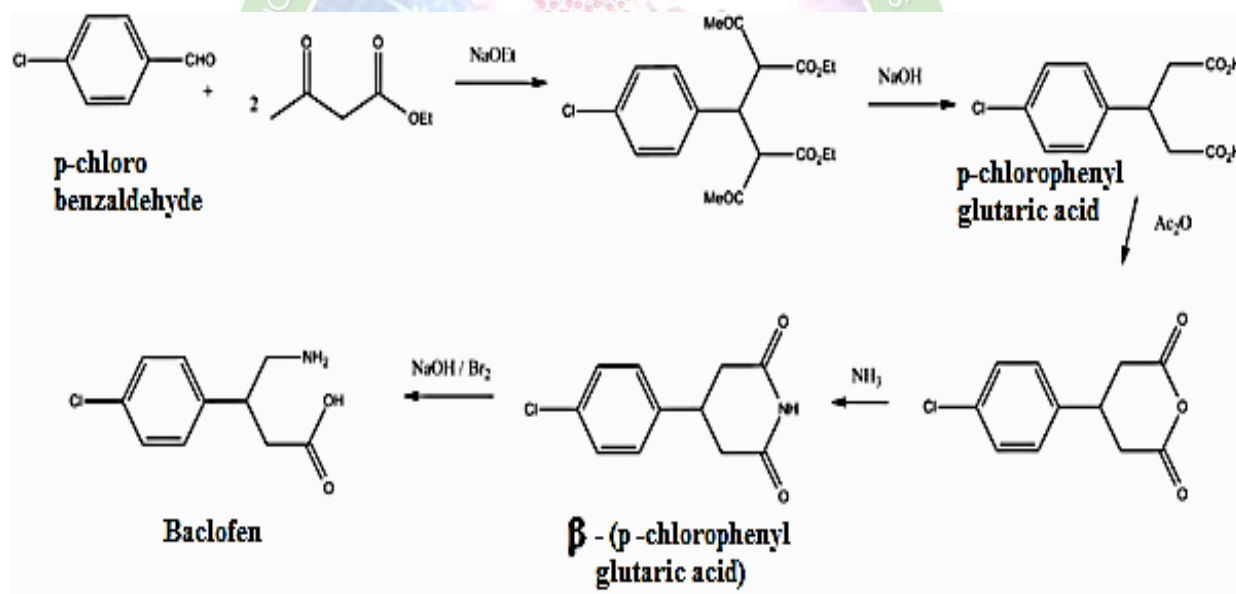


Figure 1: Synthesis of Baclofen from p-chlorobenzaldehyde [13,14]

**1.2 Degradation Products:** These impurities usually result by degradation of the end product or degradation during storage or aging.

Example:

Hydrochlorothiazide (Diuretic) has a known degradation pathway by which it degrades to its starting material i.e disulfonamide [11].

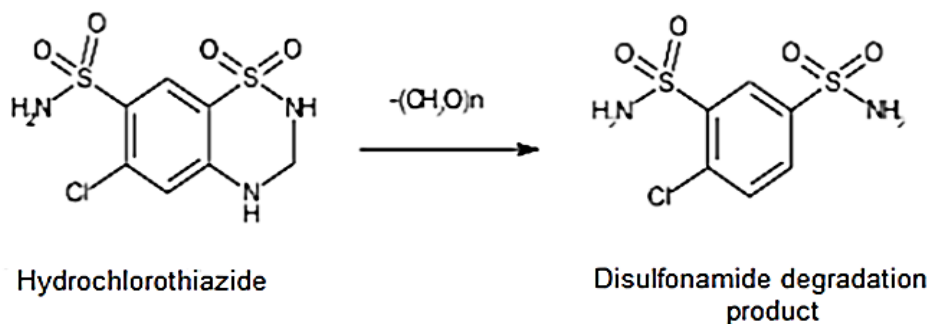


Figure 2: Degradation of Hydrochlorothiazide [11]

**1.3 By-Products:** These impurities result from a variety of side reactions, such as isomerization, dimerization, incomplete reaction, over reaction, rearrangement or unwanted reactions between the starting materials or intermediates with either chemical reagents or catalysts. Some frequently occurring side reactions, which are unavoidable, are well-known to the synthetic chemist [15].

### Products of over-reaction

In many synthetic reactions, the last steps are not selective enough and thus the reagents attack the intermediate not only at the desired site but also at the other sites[9].

Example:

During Quinapril (Antihypertensive) synthesis, the impurities were formed during the last synthetic step when either trifluoroacetic acid or HCl gas/ $\text{CH}_2\text{Cl}_2$  was used to remove the t-butyl group from the pure t-butylester precursor. Examination of the byproducts by TLC and NMR revealed that they are a complex of the drug, the corresponding diketopiperazine and two other unidentified impurities [16].

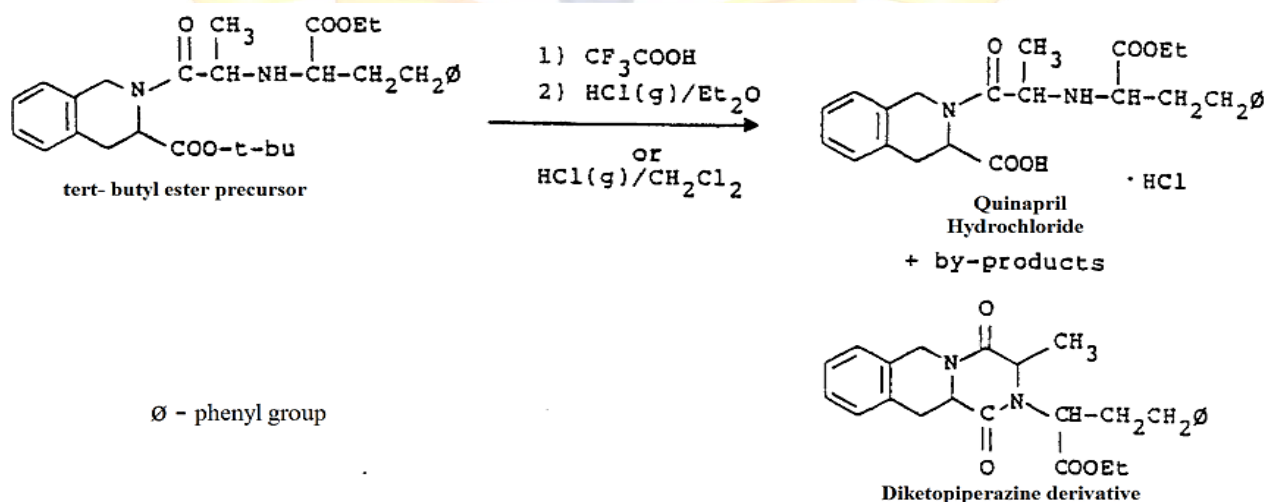


Figure 3: Synthesis of Quinapril which results in diketopiperazine derivative as one of the byproducts [16]

## 2. INORGANIC IMPURITIES:

**2.1 Reagents and Catalysts:** The occurrence of these impurities is rare. These impurities can be minimized only if proper care is taken by the manufacturer during production [17].

### 2.2 Heavy Metals:

Example: Iron catalyzed degradation of Enzastaurin (Anti-cancer) to produce the oxidative degradation product, compound 2579539 [18].

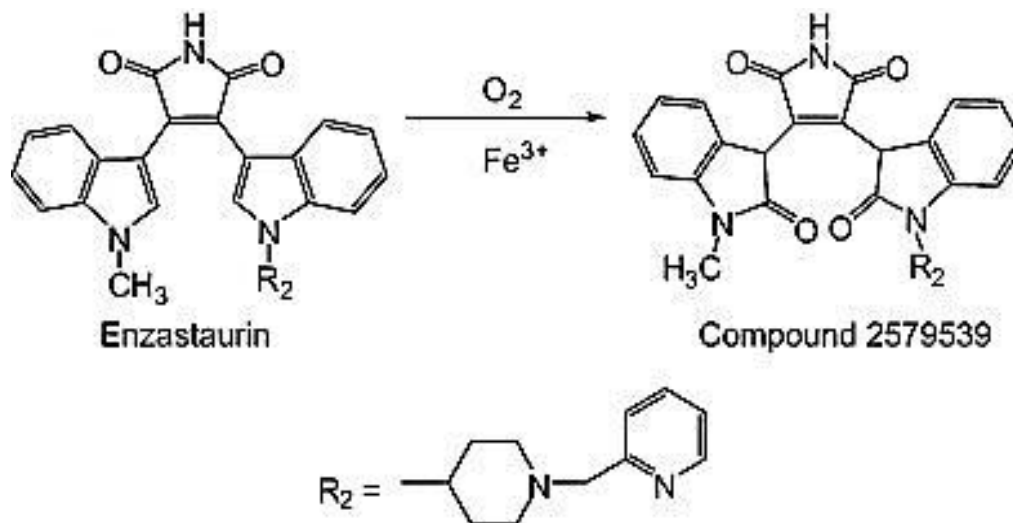


Figure 4: Iron catalyzed degradation of Enzastaurin [18]

**2.3 Other Materials:** The filtering aids such as centrifuge bags and activated carbon are routinely used in the manufacturing of bulk drugs. Thus, the regular monitoring of fibers and black particles in bulk drugs is important [17].

**3. RESIDUAL SOLVENTS:** They are potentially undesirable substances which may be hazardous to human health. They may also alter the physicochemical properties of the bulk drug substances such as crystallinity of the bulk drug, which in turn may affect the dissolution properties; odor and color changes in finished products. ICH guidelines have classified the residual solvents into four classes [11].

Table No. 2: Classification of residual solvents with examples and limits as per ICH guidelines [6,11]

CLASS OF RESIDUAL SOLVENTS	DESCRIPTION	EXAMPLES	CONCENTRATION LIMIT (ppm)
CLASS I	These solvents are not employed in the manufacture of pharmaceuticals because of their unacceptable toxicity. If their use is unavoidable, then it should be restricted.	Benzene	2 (Carcinogenic)
		Carbon Tetrachloride	4 (Toxic)
		1,1,1-Trichloroethane	1500 (Environmental hazard)
CLASS II	The usage of these solvents is limited in pharmaceutical products because of their inherent toxicity.	Chloroform	60
		Acetonitrile	410
		Methanol	3000
CLASS III	These are less toxic and possess lower risk to human health than class I or class II solvents. Long-term toxicity or carcinogenicity not reported, which is evident from the available data for the solvents under this category.	Acetic acid, ethanol, dimethyl sulfoxide	
CLASS IV	For this class of solvents, adequate toxicological data is not available. The manufacturers need to justify the residual levels for this class of solvents in pharmaceutical products.	Methyl isopropyl ketone, isopropyl ether	

## **FORMULATION RELATED IMPURITIES**

**1. DOSAGE- FORM RELATED IMPURITIES:** Before marketing the drug product, a preformulation as well as stability study is performed by the pharmaceutical industry. In spite of this, the dosage form factors sometimes may force a company to recall the product.

Example:

Fluocinonide Topical Solution USP 0.05% (60-mL bottles) was recalled because of degradation/impurities leading to sub-potency.

**2. METHOD RELATED IMPURITY:** Some impurities result during the formulation process either due to exposure to heat, light, change of pH, solvents etc [2].

Example:

A known impurity, 1-(2,6-dichlorophenyl) indolin-2-one was found in the parenteral dosage form of diclofenac sodium when it was terminally sterilized by autoclave. The condition of the autoclave method (i.e.,  $123 \pm 2^\circ\text{C}$ ) enforced the intramolecular cyclic reaction of diclofenac sodium resulting in the formation of the indolinone derivative [19].

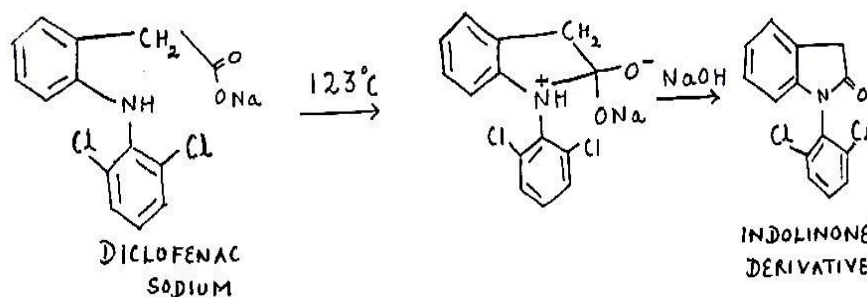


Figure 5: Intramolecular cyclic reaction of Diclofenac sodium to form Indolinone derivative as an impurity [11]

### 3. ENVIRONMENTAL RELATED IMPURITY:

**3.1 Temperature:** Many APIs are heat-labile.

Example:

Vitamins are very heat-sensitive and frequently undergo degradation leading to loss of potency especially in liquid formulations.

**3.2 Light- UV light:**

Example:

Ergometrine (Uterine stimulant) as well as methyl ergometrine injection is unstable under tropical conditions such as light and heat [12]. Only in 50% of the samples the level of the active ingredient complied with the BP/USP limit of 90% to 110% of the stated content [20].

**3.3 Humidity:** It is an important factor especially in case of hygroscopic compounds [12].

**IMPURITIES ON AGING****1. MUTUAL INTERACTION BETWEEN INGREDIENTS:**

Example:

Presence of nicotinamide in vitamin-B complex injection containing four vitamins (nicotinamide, pyridoxine, riboflavin and thiamine) causes the degradation of thiamine to a substandard level within a one year shelf life [21].

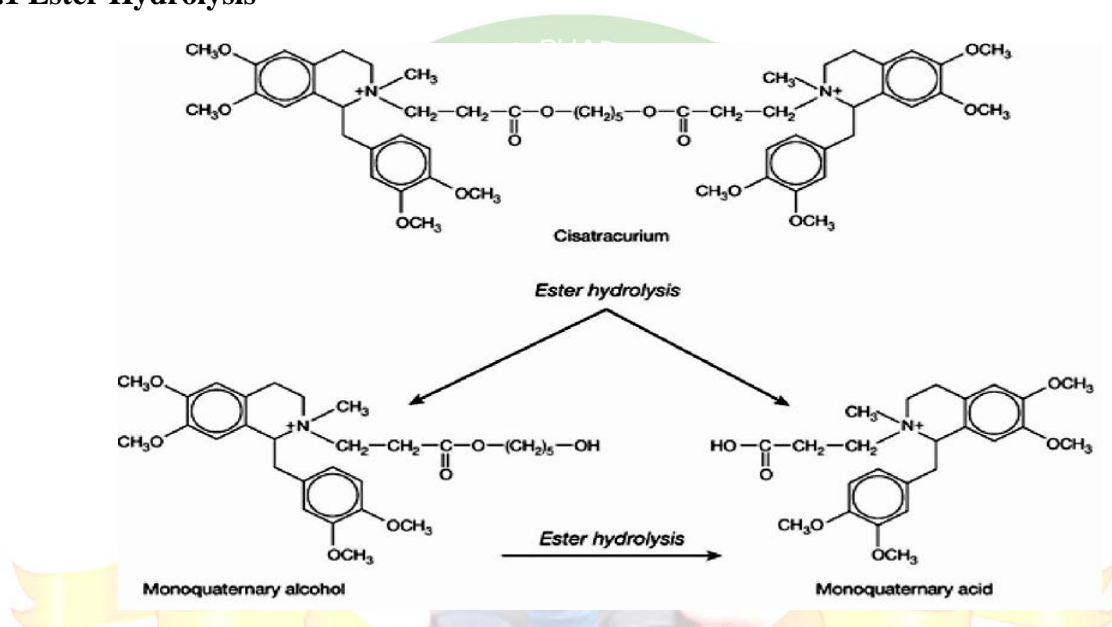
**2. FUNCTIONAL GROUP RELATED TYPICAL-DEGRADATION IMPURITIES:****2.1 Ester Hydrolysis**

Figure 6: Example: Degradation pathway of Cisatracurium (Skeletal muscle relaxant) [22]

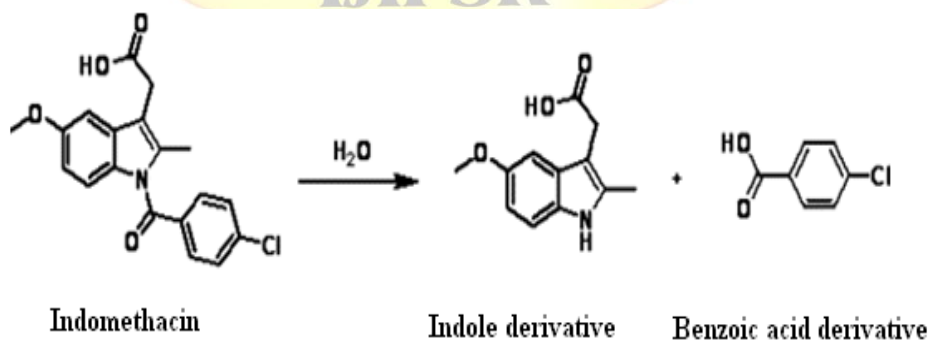
**2.2 Hydrolysis**

Figure 7: Example: Decomposition pathway of Indomethacin [23]

## 2.3 Oxidative Degradation

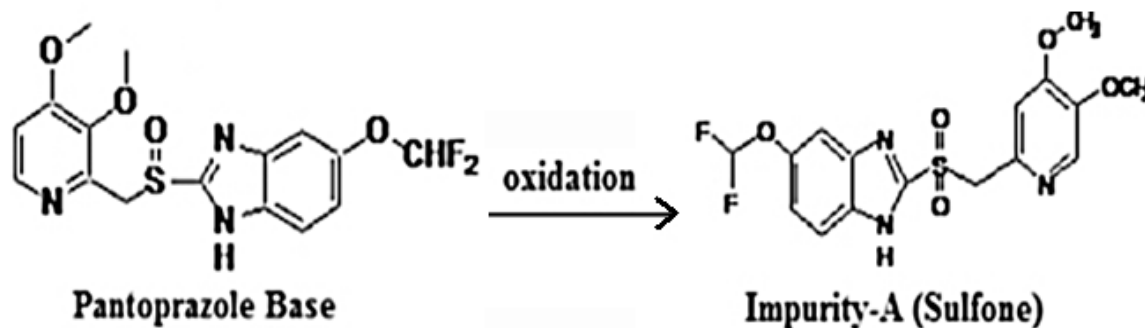


Figure 8: Example: Oxidative degradation of Pantoprazole (Proton pump inhibitor) [24]

## 2.4 Photolytic Cleavage

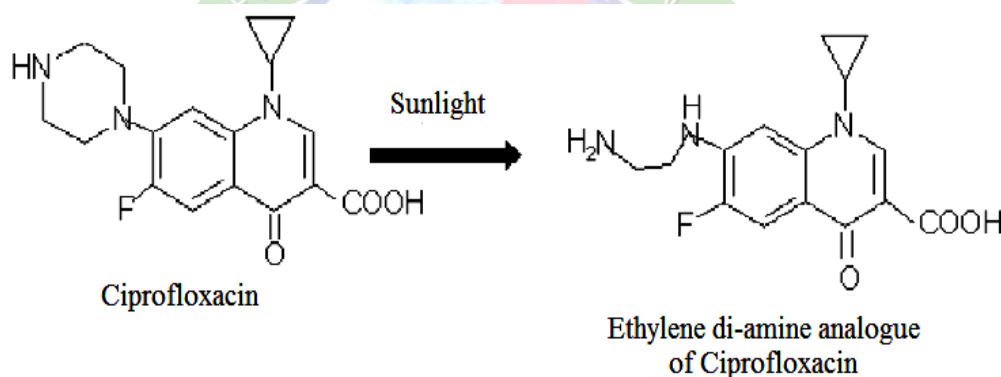


Figure 9: Example: UV light induced photolysis of Ciprofloxacin eye drop (0.3%) formulation [25]

## 2.5 Decarboxylation

Example:

The tablet of rufloxacin enteric coated with cellulose acetate phthalate (CAP) and sub-coating with calcium carbonate on undergoing photolytic reaction resulted in hydrolysis of CAP liberating acetic acid, which on reacting with calcium carbonate produced carbon dioxide, a byproduct that blew off the cap from the bottle after the cap was loosened [26].

## 3. PACKAGING MATERIAL:

Example:

Extractable or leachable – Emerge from glass, rubber stoppers and plastic materials, in which oxides like NO<sub>2</sub>, SiO<sub>2</sub>, CaO, MgO are the major components leached or extracted from glass [27].

## OTHER IMPURITIES

**1. ENANTIOMERIC IMPURITIES:** Naturally occurring biosynthetic products have a high level of enantioselectivity of their biosynthesis thus excluding the possibility of the presence of enantiomeric impurities. In the case of synthetic chiral drugs, if the pure enantiomer is administered, the other enantiomer is considered to be an impurity. This impurity may be present either due to incomplete enantioselectivity of the synthesis or incomplete resolution of the enantiomers of the racemate.

Example:

Clopidogrel sulphate (R enantiomer impurity allowed NMT 1%) [9].

**2. POLYMORPHIC IMPURITIES:** Usually, the most stable form of the drug is used in the formulation. However, unintentionally, the metastable polymorphic form may be generated either due to temperature, moisture or mechanical treatment during processing or storage of the drug product [28]. The presence of polymorphic impurities can adversely alter the stability and efficacy of the final drug product [29].

Example:

Salmeterol xinafoate exists in two crystalline polymorphic forms, Form I being the stable form and Form II the metastable polymorph under ambient conditions. Commercial salmeterol xinafoate is a micronized form which has the same crystal structure as that of Form I. However, it may contain traces of the Form II polymorph (polymorphic impurity) that is formed during the micronization process [30].

**3. GENOTOXIC IMPURITIES:** These impurities are mutagenic and could potentially damage DNA [31].

Table No. 3: Classification of genotoxic impurities [31]

CLASSIFICATION	QUALIFICATION STRATEGY
CLASS 1	Impurities : genotoxic and carcinogenic
CLASS 2	Impurities : genotoxic, but with unknown carcinogenic potential
CLASS 3	An Alerting structure, unrelated to parent structure and of unknown genotoxic potential
CLASS 4	An Alerting structure, related to the parent API
CLASS 5	Neither alerting structure nor indication of genotoxic potential

Example:

Linezolid, a new class of antibiotics i.e. oxazolidinones, has many genotoxic structural alerts [32].

## REGULATORY GUIDELINES

The different regulatory guidelines for impurities include:

ICH GUIDELINES “STABILITY TESTING OF NEW DRUG SUBSTANCES AND PRODUCTS”- Q1A

ICH GUIDELINES “IMPURITIES IN NEW DRUG SUBSTANCES”- Q3A

ICH GUIDELINES “IMPURITIES IN NEW DRUG PRODUCTS”- Q3B

ICH GUIDELINES “IMPURITIES: GUIDELINES FOR RESIDUAL SOLVENTS”- Q3C

US-FDA GUIDELINES “NDAS -IMPURITIES IN NEW DRUG SUBSTANCES”

US-FDA GUIDELINES “ANDAS – IMPURITIES IN NEW DRUG SUBSTANCES”

AUSTRALIAN REGULATORY GUIDELINE FOR PRESCRIPTION MEDICINES, THERAPEUTIC GOVERNANCE AUTHORITY (TGA), AUSTRALIA [33]

## METHODS INVOLVED IN IMPURITY PROFILING

**1. Identification Methods:** Reference standard method, Spectroscopic methods (UV, IR, NMR, MS)

**2. Separation Methods:** Chromatographic methods (GC, TLC, HPTLC, HPLC), Capillary electrophoresis

Table No. 4: Examples of impurities reported in APIs with their respective separation methods [34]

DRUG	IMPURITY	METHOD
AmphotericinB	Tetraenes	Ultra Violet Spectroscopy
Cloxacillin	N,N-dimethylaniline	Gas Chromatography

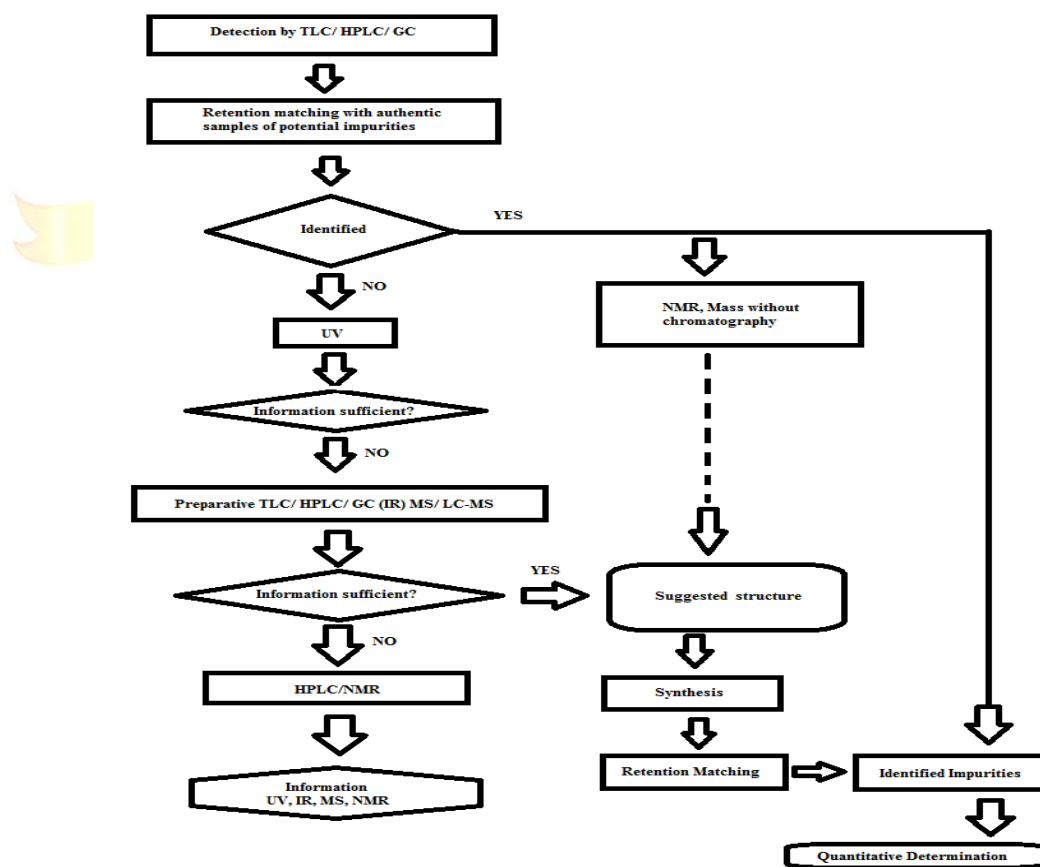
**3. Isolation Methods:** Liquid- liquid extraction methods, Supercritical fluid extraction, Accelerated solvent extraction methods, Solid- phase extraction methods.

**4. Characterization Methods:** NMR, MS, Hyphenated methods (GC-MS, LC-MS-MS, HPLC-DAD-MS, HPLC-DAD-NMR-MS) [34]

**Table No. 5: Examples of impurities reported in APIs with their respective characterization methods**

DRUG	IMPURITIES	METHOD	REFERENCE NO.
Norgestrel	Related substances	TLC, HPLC & UV spectroscopy	[35]
Celecoxib	Process related impurities	HPLC, LC-MS-MS	[36]

**5. Validation Process:** The aim of the validation process is to challenge the developed method and determine limits of allowed variability for the conditions needed to run the method [37]. The parameters of assay validation include specificity, accuracy, linearity, range, precision, robustness, limit of detection and limit of quantitation. In addition, the analysts should also examine the sample solution stability and establish an appropriate system-suitability test to verify the proper functioning of the equipment employed in performing the analysis [38].



**Figure 10: General scheme for Drug Impurity Profiling [39]**

## SIGNIFICANCE

1. It helps in identification and quantification of impurities.
2. It ensures that the impurities present are within the limits as specified under ICH guidelines.
3. With the help of modern 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).
4. It helps in establishing a control system for impurities involving processing or manufacturing conditions, suitable analytical methods/ specifications, long term storage conditions including packaging and formulation [34].
5. 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, to assure whether they are within the concentration limits as specified under ICH guidelines.
6. In case of formulation related impurities: An excipient which affects the stability of an API is thus not incorporated in the formulation of the API or the method / environmental conditions can be controlled to avoid degradation of the API.
7. In case of degradation-related impurities: The potential degradation products can be determined through stress testing and actual degradation products through stability studies. Also the degradation pathway can be determined and thus methods to minimize degradation can be developed [11,34].
8. In case of other impurities:  
  
Enantiomeric impurity: The enantioselectivity of the synthesis of the API can be determined. The presence of the correct enantiomer (responsible for therapeutic activity of the API) in the formulation can be verified [9,40].  
  
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 [30].  
  
Genotoxic impurity: The source of the genotoxic impurity can be determined (starting material/ reagents/catalyst/degradation product) and thus be prevented. The genotoxic impurity can be categorized and its risk can be determined [41].

## APPLICATIONS

Impurity profiling has wide applications in the areas of:

1. Drug designing,

2. Monitoring stability and quality, and
3. Safety of pharmaceutical compounds [9,12].

### 1. Drug Designing:

Determining the structures of degradation products arising during forced degradation study i.e. stress testing can be useful for preclinical discovery efforts during structure-activity relationship investigations. An understanding of the various parts of the molecule that are susceptible to degradation can also help in the design of more stable analogs. The development of a stable formulation is also aided by an understanding of the reactive parts of the drug molecule [42].

Example:

Impurity profiling of Ezetimibe was carried out. Ezetimibe was found to be stable in acidic, oxidative, thermal and photolytic stress conditions. Extensive degradation of Ezetimibe occurred only in alkaline hydrolytic conditions [43]. This may be because of the decomposition of the  $\beta$ - lactam ring under alkaline conditions. With the help of computer models, newer analogues were developed by using alternative rings that would hold the other fragments of the molecule in a similar orientation as those in the active drug [44].

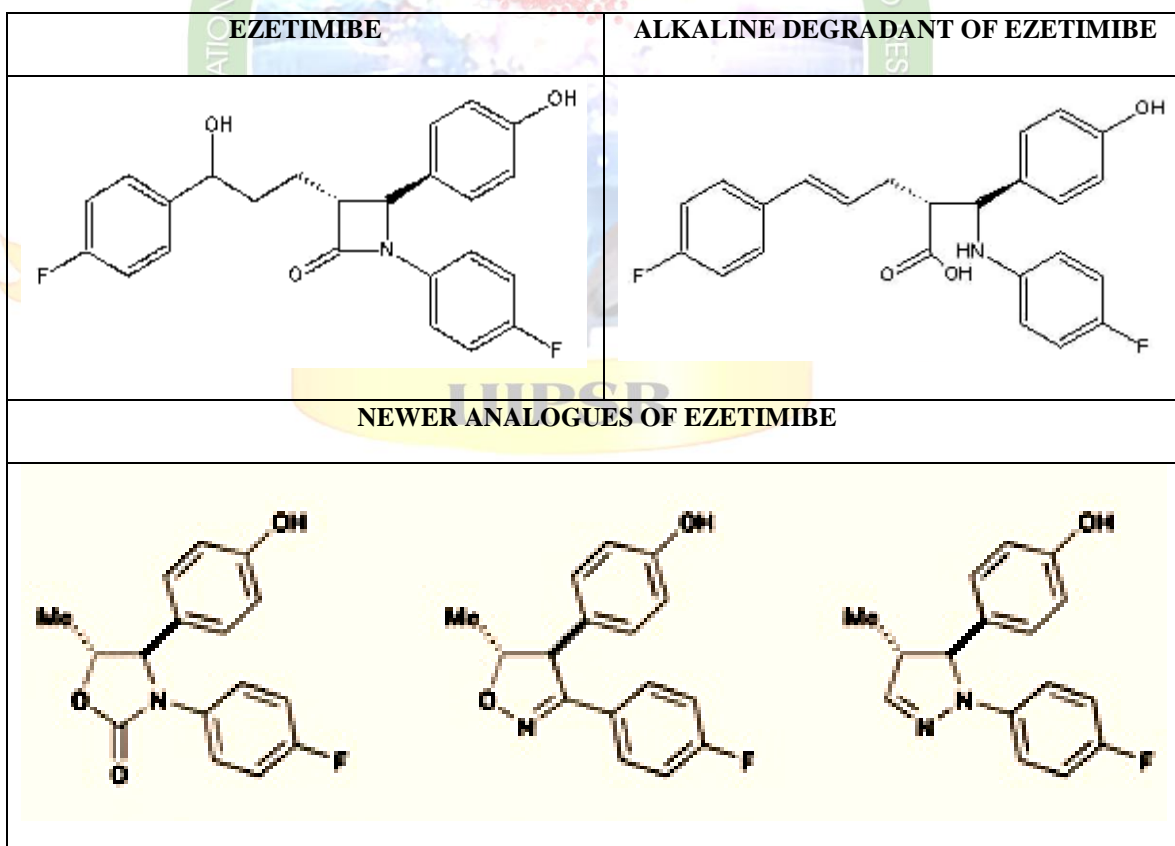


Figure 11: Chemical structure of Ezetimibe, its alkaline degradant and its newer analogues [42,43]

## 2. Monitoring Stability and Quality:

Isolation and elucidation of the structures of degradation products are typically collaborative research involving analytical, organic and physical chemistry knowledge combined with spectroscopic information. When this process is performed at an initial stage, there is ample time to address various aspects of drug development to prevent or control the production of impurities and degradation products well before the regulatory filing and thus ensure production of a high-quality and highly stable drug product [42].

## 3. Monitoring Safety:

In case of a genotoxic impurity, impurity profiling is a critical activity. It involves the identification, classification, qualification of structural alerts as genotoxic impurities and finally demonstrates their control in the drug substance and thus helps in monitoring its safety [31].

## CONCLUSION

Impurity profiling is extremely vital during the synthesis and manufacturing of drug substances (API) and drug products, as it helps in providing crucial information relating to the limit of detection, limit of quantification and also the toxicity limit for different types of impurities. Various regulatory guidelines have outlined the limits for the different types of impurities that are required to be complied with.

An accurate method development and validation of the procedures makes the impurity profiling task easy. Thus, with the assistance of the impurity profile study, it becomes convenient to design such a method and product wherein the expected impurity cannot interfere.

## FUTURE PROSPECTS

The ICH as well as the other regulatory bodies has outlined guidelines with regard to impurities but there is a strong requirement to have unified specifications/standards for regulation of impurities. There is also a need for the development of more rapid, specific, sensitive and cost-effective methods for isolation and characterization of impurities.

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