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Comprehensive Study about the Approaches of Building up Impurity Profiling from an Industrial Viewpoint

Souvik Kundu[1],Debraj Paul[2],Rahul Patra[3],Jaydip Ray[4]

[1,2,3&4]Department of Pharmaceutical Quality Assurance, Guru Nanak Institute of Pharmaceutical Science and Technology, West Bengal, Kolkata, India

Corresponding author: **Jaydip Ray**

Abstract

In the field of health research impurity profiling carries a crucial job in drug safety, efficacy, and quality. Impurities may be incorporated with drug or pharmaceutical molecules in any stage of manufacturing including the time of synthesis, processing, storing, degrading due to environmental factors, or in the time of transportation of APIs. Indeed, even in trace amounts, it very well may involve issues with the dosage form. To overcome impurity problem, profiling is mandatory and includes steps like identification, isolation, characterization, quantification, and separation. Major sophisticated instruments like chromatography, spectroscopy are involved in this process. Impurity profiling helps in identifying the drug's compatibility, stability concern, microbial activity, interactions, or degradation pathways and furthermost the related harmfulness profile. Thus, it is helps in up-regulation of shelf life of product. Global bodies like USFDA, EU, TGA, and EMA are involved in monitoring and responsible for introducing guidelines and SOPs to minimize and control the impurity in between acceptance ranges. Globally, for the pharmaceutical field, it is a major worry of research and continuous advancements are made in analytical methodologies for more critical and updated characterization by which accurate assessments are finished and minimize impurity as well as possible throughout the product life cycle. This comprehensive study examines the various approaches used in the industrial setting to build up impurity profiling. The study explores the analytical techniques, strategies, and considerations involved in identifying, characterizing, and quantifying impurities. It also discusses the challenges faced by industrial practitioners and the emerging trends in impurity profiling.

Keywords – APIs, USFDA, EMA, Spectroscopy, Toxicity profiling, SOPs.

Introduction

In the pharmaceutical industry Impurity profiling is an essential validation process of the quality control for Active Pharmaceutical Ingredients (APIs) and drugs [1]. It involves the process of identification and quantification of impurities as well as the

related methods of purification of impurities that may be attending in the drug or APIs substances. It is a serious concern in the aspect of healthcare sector where the adverse effect of drugs can result in a fatal outcome [1, 2]. Patient safety is the primary objective in the treatment process, so the related process should be done perfectly. So, impurity profiling is a very serious aspect of treatment issues. Besides this many other key factors are also associated with impurity profiling. Such as providing information about possible contaminants, compatibility, stability parameters, and the area of improvement of existing molecules leads to a new drug development process [3].

Some major causes led to growing up interest in impurity profiling can be described below:

- The structural elucidation of different types of impurities is a very much essential factor for the manufacturing technology of an existing drug molecule. It is the predetermined step by which the compatibility and stability of the final product can be determined. It also indicates the number of degradation possibilities and reactions to various environmental factors [3, 4]. This study thus helps the manufacturer for reduction of the number of impurities by obtaining suitable methods of separation techniques within acceptable limits.
- It is the evidence of structural elucidation of different substances present in APIs which is previously done by spectroscopy and helps in the final validation of the product [5].
- During impurity profiling the materials which pass the acceptance criteria can be used as a standard or ideal product by which related development process improvement can be enhanced. In the case of quantification, this standard provides a brief idea about the process-related impurity sources.
- The major impurities can be a good objective of the toxicological study of the drug which greatly impacts the effectiveness and protection of the therapeutic effect.
- Impurity profiling is one of the valid pieces of evidence about the consistency, stability, and efficacy-related issues before the regulatory authorities and it is also a validation report of the process of manufacturing [5, 6].
- The pharmacokinetics and pharmacodynamics study and the alteration study can be done with the help of impurity profiling.
- The regulatory approval is depending upon the impurity profiling report. Failure of passing the impurity specifications may lead to the termination of the manufacturing licensees and declare clear the products of substandard quality. It also caused legal action against the manufacturing company.
- The high level of impurity contents may lead to face a huge loss for the company as customers can reject the product due to the presence of substantial elements [7].

Arisen of impurities is a very common thing in the pharmaceutical manufacturing industry. It has a frequent source that can affect the product stability, compatibility, and efficacy, and creates safety concerns related to the treatment process. The sources include the degradation of products due to environmental factors like sunlight, humidity, temperature, contaminants due to microbial activity, residual solvents, and excipients, the interaction between components is mostly observed [8]. As the impurities are not the integral component of use these have to be eliminated by many several processes. It can be done by mechanical methods or separation methods. Firstly, the impurities present in the APIs are isolated and then it is separated by applying separation techniques. Once the impurities are separated their structural elucidations as well as quantification are being done. This is the process of validating the raw API purity. The quantification study is the parameter of the percentage of purity of APIs. There are many sophisticated instruments available for detecting impurities of APIs [9]. These analytical tools such as "High-performance liquid chromatography (HPLC), Mass spectroscopy (MS), Gas chromatography (GC), Nuclear magnetic resonance (NMR), LC-MS, FT – IR", etc. This instrument also characterizes different elements based on their structure and nature. With this feature methods of separation can be implemented readily. This type of advantage is the impurity profiling in a comprehensive validating analytical tool of continuous development. Therefore, quality control of impurities is a serious concern for manufacturing and effectiveness purposes [10].

Objective of Study

The main motto of build-up impurity profiling in the pharmaceutical industry may be as below:

- To figure out several types of impurities in APIs and determination of chemical structure as well.
- To determine the number of impurities, present in APIs.
- Ensure the impurities are present within acceptable limits as specified.
- To identify the source of impurities and incorporation impact on the efficacy as well the adverse effect of the drug.
- To monitor the process of manufacturing by which the impurities are controlled within the specific limit throughout the process and intended not to increase these.
- To develop essential methods for isolation, identification, and quantification of impurities.
- To establish the guidelines, specifications, nature of impurities, and acceptance limit for impurities.
- To examine the pharmacokinetics and pharmacodynamics study of the drug in the presence of different limits of impurities.

- To evaluate the compatibility and stability studies of the APIs substance in the presence of impurities.
- To enrich the quality of the drug substance while reducing the production of contaminants during the manufacturing process.

Classification of Impurity with Possible Sources

The classification of impurities is done based on two major regulatory guidelines which are the USP monographs and ICH schedules.

USP MONOGRAPH	ICH SCHEDULE
1. Impurities in Official Articles	1. Organic Impurity
2.Ordinary Impurity	2. Inorganic Impurity
3.Organic Volatile Impurity	3. Residual Solvents

Table 1. Impurity classification as per USP & ICH [11]

Though the above guidelines are useful to categorize the impurity present in drugs or pharmaceutical products, there are several other possibilities for occurring and incorporating impurities with the product. Thus, a brief classification and sources also needed to be coined properly by which each category of impurity can be identified separately [11, 12].

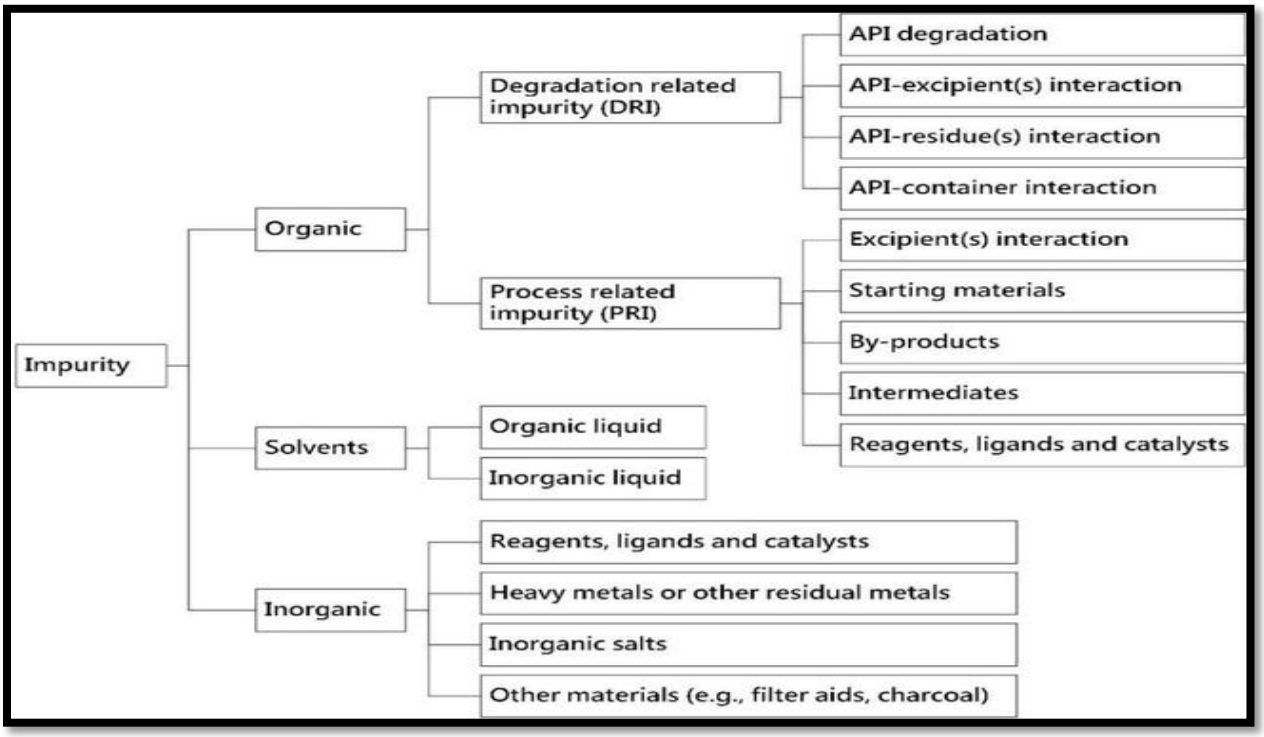

Table 2.Brief Classification& Sources of Impurities at Industrial Zone [11]

Common Analytical Techniques for Impurity Profiling in the Industry

- **Extraction Techniques**
  - Solid-phase extraction methods
  - Liquid-liquid extraction methods
  - Accelerated solvent extraction methods
  - Supercritical fluid extraction
- **Chromatographic Techniques**
  - High-Performance Liquid Chromatography (HPLC)
  - Gas Chromatography (GC)
  - Ion Chromatography (IC)
  - Ultra-performance liquid chromatography (UPLC)
  - Flash chromatography (FC)
  - Capillary electrophoresis (CE)
  - Supercritical fluid chromatography (SFC)
- **Spectroscopic Techniques**
  - Fourier Transform Infrared Spectroscopy (FTIR)
  - Ultraviolet-Visible Spectroscopy (UV-Vis)
  - Nuclear Magnetic Resonance (NMR)
  - Mass Spectrometry (MS)
- **Hyphenated Methods:**
  - LC-MS-MS
  - HPLC-DAD-MS
  - HPLC-DAD-NMR-MS
  - GC-MS
  - LC-MS
  - [12,13]

Approaches towards Building up Impurity Profile in the Industry

- **Identification of Stages of Impurity Incorporations**

  The introduction of impurities or unintended materials in a drug substance or finished pharmaceutical product may be involved several steps. It can be in starting of a process or it may also occur during transportation. Generally, it can be stated by the following table [14];

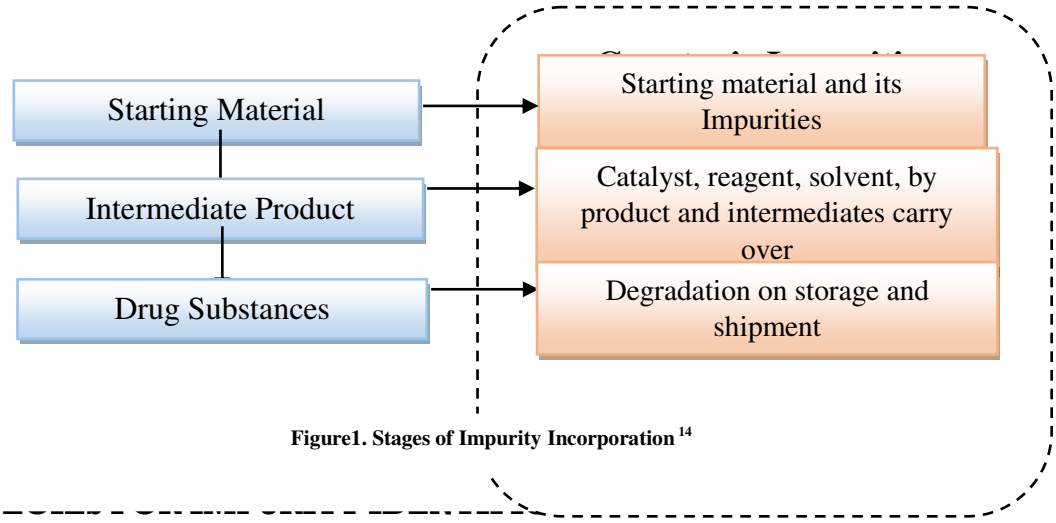

Figure1. Stages of Impurity Incorporation [14]

❖

- Comparing with Reference Standards
- Retention Time Matching
- Spectral Library Search
- Mass Spectral Interpretation
- Elemental Analysis

○ **Comparing with Reference Standards**

The Reference Standard method is a clarification about the qualification as well as the life cycle of the product. It is a benchmark by which the evaluation process is done. It thus indicates the product performance and safety concerns for therapeutic applications. Reference standard method covers all types of products for the brief study of raw APIs, degradation, intermediate, and excipients [14, 15].

○ **Retention Time Matching**

Retention time matching is a chromatographical technique, which can be used technique used for separation and analyzing purposes [16]. It does the comparison between the retention times of two different chromatograms going through the same experimental consideration. These reference standards are made of pure components having known retention time value. The comparison study of retention time peaks of standards and the sample will depict the identification of components in the sample mixture [17].

○ **Spectral library search**

It involves a comparison between the mass spectra of an unknown sample and reference mass spectra previously present in the spectral library [18]. It involves Data Acquisition, Building of a vast number of reference mass spectra, comparison study, and potential identification of unknown samples. Different Mass spectrometry techniques like Liquid chromatography-mass spectrometry

(LC-MS), Gas chromatography-mass spectrometry (GC-MS), and Tandem mass spectrometry (MS/MS or MS2) are commonly used.

- **Mass Spectral Interpretation**

  This is an analytical interpretation process by which data obtained from mass spectroscopy has emphasized to depict the structural elucidation and composition by calculating the mass-to-charge ratio (m/z) of ions. Mass Spectral Interpretation has several steps Ionization, Mass Analysis, Mass Spectrum, Molecular Ion (Parent Ion), Fragmentation Pattern, Isotopic Pattern, Interpretation and Identification, and Structure Elucidation [19, 20].

- **Elemental analysis:**

  This technique involves the determination of elemental components in a sample. It determines various elements such as carbon, oxygen, hydrogen, etc. The elemental analysis involves sophisticated machinery and some critical methods like Combustion Analysis, Inductively Coupled Plasma Optical Emission Spectroscopy (ICP-OES), Inductively Coupled Plasma Mass Spectrometry (ICP-MS), X-ray Fluorescence Spectroscopy (XRF), Carbon-Hydrogen-Nitrogen (CHN) Analyzer, Total Organic Carbon (TOC) Analysis. Therefore it is a method of analytics of composition, purity, and characterization [21, 22].

❖ **Impurity Characterization**

- **Structure Elucidation**

  - **Nuclear Magnetic Resonance**

    The NMR is a powerful analytical instrument that can generate information about the stereochemistry of molecules as well as bonding structure with specification, which are much-needed steps toward structural elucidation [22, 23]. The NMR can differentiate between monomeric and dimeric substances based on their diffusion coefficient. Although it less sensitive than other analytical instruments [24].

  - **Mass Spectrometry (MS)**

    Over the past decade, mass spectrometry has had a great impact in the field of characterization, monitoring, qualification, and quantification of related substances present in APIs and formulations [25]. It can be used in combination with Liquid Chromatography (HPLC-TLC and HPLC-CE, HPLC-MS or HPLC-NMR), Gas Chromatography (GC-MS) for obtaining information reach chromatogram. It is used vastly for its higher sensitivity and accurate result determination [26].

- **Stability Studies**

  This study is very much crucial from the industrial point of view as it involves several experiments in different environmental conditions (in-house artificial) by which the determination of shelf life, storage behavior, finished product packaging, degradation study microbial activity, and compatibility study are validated [26,27]. The responsible regulatory authority The International Council for

Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) introduces and regulates guidelines for conducting stability studies. It includes monitoring several parameters like-Physical attributes, Chemical attributes, Microbiological attributes, etc [28].

- **Forced Degradation Studies**

It is a major process in the drug development stage in which the drug substances are introduced in various stress conditions and forced fully subjected to degradation [29]. It is useful for the identification of degradation pathways, degraded products, the timing of degradation, range of temperature, pressure, humidity, light, and lastly impurity products. It introduces various phase conditions like Hydrolysis, Oxidation, Thermal stress, Photo-stability Humidity, etc .It thus, useful to determine stability profile and long-term storage assassination [30].

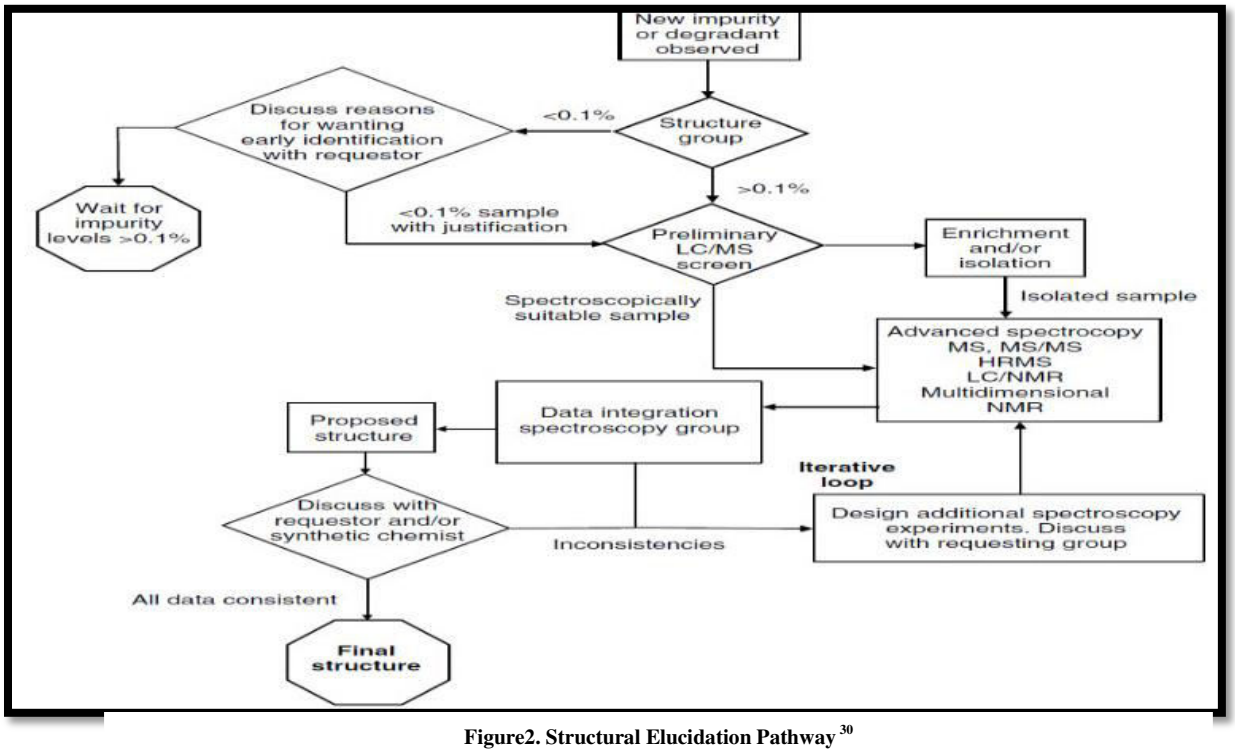

Figure2. Structural Elucidation Pathway [30]

5. Quantification of Impurities

- **External Standard Calibration**

It is a commonly used analytical technique that involves comparison studies between the concentration of unknown analysts and known standards [30]. It involves instrumentation like HPLC, GC, UV-Vis, IR, and other quantitative analysis methods. The methods included in external standard calibration are the Preparation of standard solutions, Instrument calibration, Measurement of an unknown sample, Calibration curve, Quantification of unknown, and Internal Standard Calibration [30, 31].

- **Internal Standard Calibration**

  It is a quantitative technique that involves an internal standard compound that determines the unknown concentration of an analyte in a sample [32]. The internal standard has structural similarity with the analyte. The working principle involves several steps for execution. These steps are- Selection of internal standards, Preparation of standard solutions, Sample preparation, Instrument analysis, construction of calibration curve, etc [33].

- **Spiking Studies**

  The name of this study is recovery studies or fortification studies. This involves the evaluation of the analytical method in the context of accuracy and precision in the recovery of an analyte that was added to a known sample [34].

  The working principle involves-Prep mple Determination of baseline analyte concentration, Spiking the sample, Sample preparation and analysis, Calculation of recovery, Statistical analysis, etc [35,36].

Table 3. Maximum allowable impurity limit for an API in a dosage form [30]

Brief Pathway of Impurity Declaration in Industrial Viewpoint

❖ **Impurity Tolerance Range Determination**

From an industrial perspective, all other materials incorporated with the APIs or Lead compound are not declared as an impurity unless they may lead to form an adverse effect and also cross the tolerance range [37]. There is a guideline introduced by ICH in which the range and threshold quantity parameters are indicated [37, 38].

Threshold	MDD* of API in drug Product	Threshold limit based on TDI**
Reporting	≤1g	0.1%TDI
	>1g	0.05%TDI
Identification	<1mg	1.0%TDI or 5µg
	1mg-10mg	0.5%TDI or 20 µg
	10mg-2g	0.2%TDI or 2mg
	>2g	0.1%TDI
Qualification	<10mg	1.0%TDI or 50µg
	10mg-100mg	0.5%TDI or 200µg
	100mg-2g	0.2%TDI or 3mg
	>2g	0.1%TDI

*MDD: Maximum daily dose; **TDI: Total daily intake

- **Declaration Pathway**

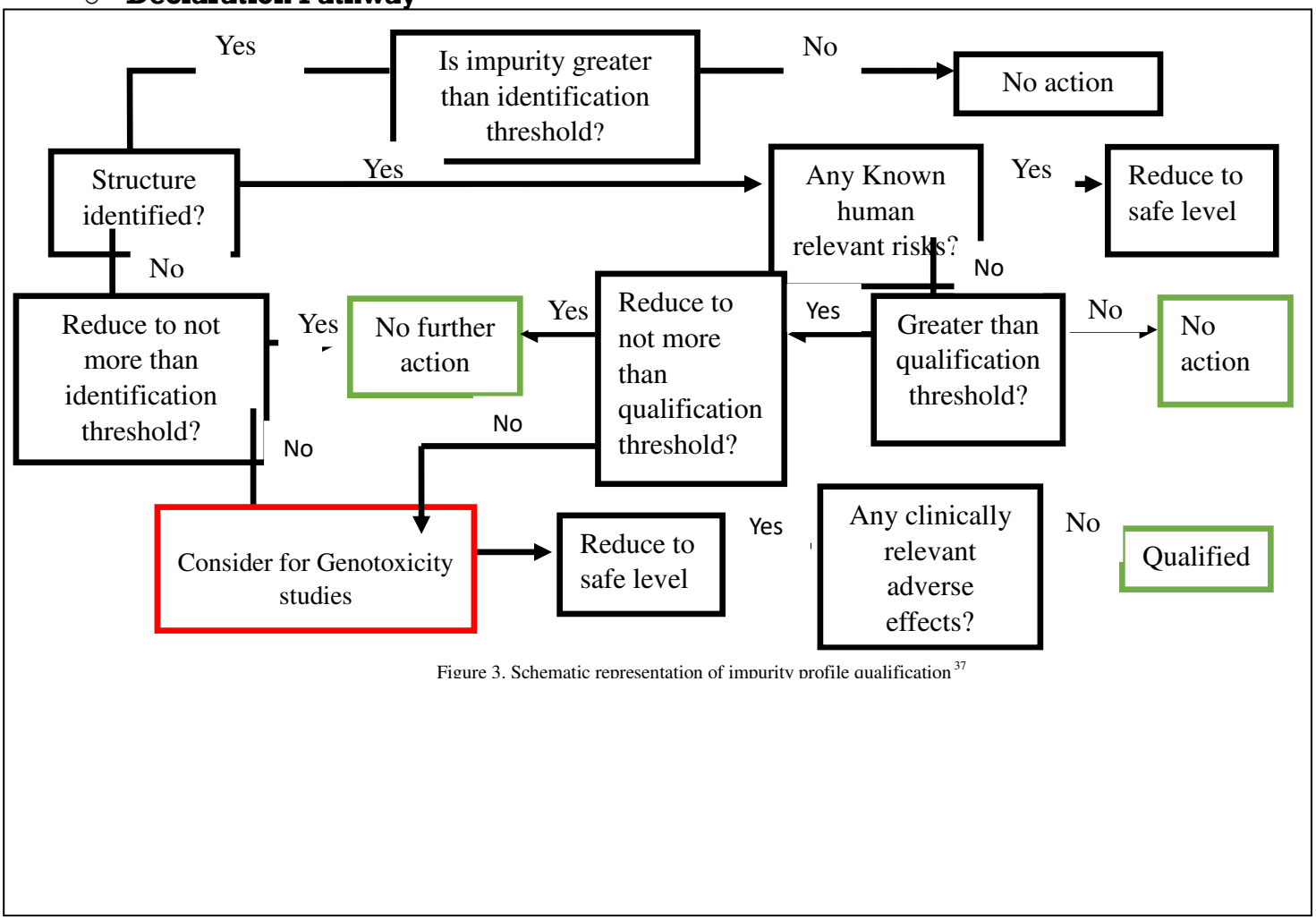

Figure 3. Schematic representation of impurity profile qualification [37]

- Time and Cost Constraints

❖ **Complex Sample Matrices**

Generally, industrial working materials or samples have complex matrices which consist of several ingredients which can produce difficulties in the process of identification, quantification as well as qualification of impurity profiling [39,40]. It is a challenging work for the person to extract and separate the matrix from the product. Thus, it needs great techniques and updated sophisticated types of machinery [41].

❖ **Low-Level Impurities**

Some impurities are present in trace amount yet cause a severe adverse effect on human health if remains in the final product [42]. For such impurities, detection is relatively tough because of their lower concentration in the product. It requires highly sensitive analytical techniques for accurate detection with a defined limit range (43).

- **Co-elution and Peak Overlapping**
  If the impurity materials are quite the same kind in nature then co-elution can be possible as they bear with same attraction theory [43, 44]. So, it may also lead to the overlapping of peaks in the final chromatogramatical paper.
- **Stability and Storage Considerations**
  In maximum cases, misleading information about degradation pathways and kinetics are played as the key factor behind the instability of the product [45]. So understanding this with professionalism is a much-needed criterion for a responsible one. Beside this, stability study demands all types of condition coordination which is a tough challenge for an organization to arrange such things as desire [46].
- **Regulatory Requirements**
  For the industrial perspective, Impurity profiling is vital validation proof of the quality. So maintaining quality guidelines up-to-date is a matter of need, but can be difficult as it can vary across different climates and environmental issues [47].
- **Time and Cost Constraints**: Impurity profiling is a costly investigation that requires time, skill, specialized instruments, and experience in handling with proper knowledge. Performing impurity profiling within tight timelines while balancing cost constraints can pose challenges for industrial manufacturers [48, 49, 50].

Conclusion

In a conclusive statement, impurity profiling from the industrial context is a crucial aspect of pharmaceutical analysis and quality control. It ensures product quality, safety, and efficacy of pharmaceutical products by identifying, quantifying, and characterizing impurities. Although the industry has to face challenges in the field of sensitivity and detection limits, method development and validation, impurity identification, sample complexity, stability and degradation, regulatory requirements, time and cost constraints, and process-related impurities [51,52,53].

For these cause critical analytical techniques and sophisticated instruments are evolved which can detect and separate trace amounts of impurities. The regulatory guidelines and proper SOPs of process development Quality Control play a vital role in these contexts [54].

By implementing appropriate quality measures pharmaceutical companies can be minimized impurity and patient safety. Regulatory authorities require impurity profile-ling as part of the drug approval process to ensure compliance with quality standards. Continuous improvement, staying updated with industry regulations, and investing in research and development are key to overcoming the challenges and achieving successful impurity profiling in the industrial context [55].

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Conflict of Interest

The authors declare that they have no conflict of interest for this study.

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