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Identifying the Impurity Profiling for Pharmaceutical Product by Using Different Analytical Techniques: A Overview

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Review Article

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ABSTRACT

Impurity profiling brings tremendous efforts in the group of analytical activities, the aim of which is the detection, identification/structure elucidation and quantitative determination of organic and inorganic impurities, as well as residual solvents in bulk drugs and pharmaceutical formulations. The control of impurities is currently a critical issue to the healthcare manufacturing. Various regulatory authorities like ICH, USFDA, UK-MHRA, CDSCO are emphasizing on the requirements and the identification of impurities in Active Pharmaceutical Ingredient's (API's) and as well as finished products. On the beginning of hyphenated techniques, the most browbeaten techniques for impurity profiling are Liquid Chromatography (LC)-Mass Spectroscopy (MS), LCNMR, LC-NMR-MS, GC-MS and fully automated Comprehensive Orthogonal Method Evaluation Technology (COMET). That is why it has plentiful claim in the field of drug design, monitoring quality, stability and as well as safety of the product.

INTRODUCTION

Over the last few decades there was much interest was compensated towards the quality of pharmaceuticals that enter into the market. The source of Active Pharmaceutical Ingredient (APIs) of specific quality of the bulk drug industry which forms the base of all formulation-based pharmaceuticals. So, it is obligatory to carry out dynamic quality control checks in order to uphold the quality and purity of output from each industry. Impurity of pharmaceuticals may produce at any stage; it may occur during synthesis, storage, due to side reaction,

degradation, changes of any physiochemical property upon storage [1]. So, stability study of pharmaceutical also play key role in the field of impurity profiling. Impurities present more than 0.1% should be identified and quantified by selective methods.

Impurity is defined by ICH as any component of the new drug substance which is not the chemical entity defined as the new drug substance or any component of the drug product which is not the chemical entity defined as the drug substance or an excipient in the drug product." Impurity profiling is a group of analytical activities for detection, isolation identification/structure elucidation, Quantitative determination of organic and inorganic impurities and residual solvents in bulk drugs and pharmaceutical formulations.

Guidelines for the control of pharmaceutical impurities

This document provides guidance for registration applications on the content and qualification of impurities in new drug products produced from chemically synthesised new drug substances not previously registered in a region or member state.

Scope of the guideline

This guideline addresses only those impurities in new drug products classified as degradation products of the drug substance or reaction products of the drug substance with an excipient and/or immediate container closure system (collectively referred to as "degradation products" in this guideline). Generally, impurities present in the new drug substance need not be monitored or specified in the new drug product unless they are also degradation products (see ICH Q6A guideline on specifications). Impurities arising from excipients present in the new drug product or extracted or leached from the container closure system are not covered by this guideline. This guideline also does not apply to new drug products used during the clinical research stages of development. The following types of products are not covered in this guideline: biological/biotechnological products, peptides, oligonucleotides, radiopharmaceuticals, fermentation products and semisynthetic products derived therefrom, herbal products, and crude products of animal or plant origin. Also excluded from this document are:

- Extraneous contaminants that should not occur in new drug products and are more appropriately addressed as Good Manufacturing Practice (GMP) issues.
- Polymorphic forms
- Enantiomeric impurities

Analytical technologies for impurity profiling in pharmaceutical development

Impurity profiling includes identification, structure elucidation and quantitative determination of impurities and degradation products in bulk drug materials and pharmaceutical formulations. Impurity profiling has gained importance in modern pharmaceutical analysis due to the fact that unidentified, potentially toxic impurities are hazardous to health and in order to increase the safety of drug therapy, impurities should be identified and determined by selective methods. Impurities in pharmaceuticals are unwanted chemicals that remain with the Active Pharmaceutical Ingredients (APIs) or develop during formulation or upon aging of both API and formulation. In the pharmaceutical industry, an impurity is considered as any other inorganic or organic material, or residual

solvents other than the drug substances, or ingredients, that arise out of synthesis or unwanted chemicals that remains with APIs.

The presence of these unwanted chemicals even in trace amount may influence the efficacy and safety of pharmaceutical product. EPR spectroscopy detects and identifies traces of transition metals, monitors drug degradation processes that produce and involve free radicals and observes the production of free radicals catalysed by transition metals or other impurities.
Impurities can be classified into the following categories:

- Organic Impurities (process and drug related).
- Inorganic impurities.
- Residual solvents.
- Organic impurities

It can arise during the manufacturing process and/or storage of the new drug substance. This organic impurity can be identified or unidentified, volatile or nonvolatile and also include:

- Starting materials
- By-products
- Intermediates
- Degradation products
- Reagents, ligands and catalysts

Inorganic impurities

Inorganic impurities are usually detected and quantified using pharmacopeial or other appropriate principles. Carryover of catalysts to the drug substance should be evaluated throughout development. These kinds of impurities can result from the manufacturing progression. These are normally known and identified and include:

- Reagents, ligands and catalysts
- Heavy metals or other residual metals
- Inorganic salts.
- Other materials (e.g., filter aids, charcoal)

Residual solvents

Solvents are inorganic or organic liquids used as vehicles for the preparation of solutions or suspensions in the synthesis of a new drug substance. The control of residual solvents used in the manufacturing process for the drug substance should be discussed. Acceptance criteria must be based on pharmacopeial standards, or ICH (Q3C) guidelines or known safety data, depends on the dose, duration of treatment, and route of administration. Depending on the possible risk to human health, residual solvents are divided into three classes.

Limits for impurities

According to the ICH guidelines on impurities in new drug products, identification of impurities below 0.1% level is not measured to be necessary, unless otherwise potential impurities are expected to be unusually potent or toxic. According to the ICH, the maximum daily dose qualification threshold to be considered is as follows (Table 1)

Table 1. Drug substance impurities thresholds.

Maximum daily dose	Reporting	Identification threshold	Qualification threshold
≤ 2 gm/day	0.05%	0.1% or 1.0 mg/day intake (whichever is lower)	0.15% or 1.0 mg/day intake whichever is lower
>2 gm/day	0.03%	0.05%	0.05%

Sources of impurities

From the earlier discussion, it is clear that impurities can originate from several sources; such as;
Crystallization-related impurities

- Stereochemistry-related impurities
- Impurities arising during storage
- Method related impurity
- Residual solvents
- Synthetic intermediates and by-products
- Functional group-related typical degradation
- Mutual interaction amongst ingredients qualification of impurities

Qualification is the process of acquiring and evaluating data that establishes the biological safety of an individual degradation product or a given degradation profile at the level(s) specified. The stage of any degradation product presents in a new drug product that has been tolerably tested in safety and/or clinical studies would be considered qualified an impurity is considered qualified when it meets one or more of the following conditions:

- When the impurity is a significant metabolite to the drug substance.
- When the observed level and the proposed acceptance standard for the impurity are adequately justified by the scientific literature.
- When the observed level and proposed acceptance criterion for the impurity do not exceed the level that has been adequately evaluated in comparative *in vitro* genotoxicity studies.

Higher or lower thresholds for qualification of degradation products can be appropriate for some individual new drug products based on scientific rationale and level of concern, including drug class effects and clinical experience.

Analytical methods for identification of impurities

- The impurities can be identified by following different methods like
- Reference standard method
- Spectroscopic method
- Separation method
- Isolation method
- Characterization method
- Reference standard method

The main purpose of this method is to afford clarity on the whole life cycle, qualification and control of reference standards used in development and control of new drugs is very important. As because the reference standards provide the basic information for evaluating process and product performance of drug substances, drug products, impurities, degradation products, starting materials, intermediates, and excipients.

Spectroscopic methods

The UV, IR, MS, NMR and Raman spectroscopic methods are abundantly used for the identification of impurities. Now a day's ICP MS also play a vital role for the identification of impurities. And it has wide choice throughout the different regulatory authority. The separation method includes chromatographic techniques like TLC, HPTLC, HPLC, Gas Chromatography (GC), Supercritical Fluid Chromatography (SFC), Electrophoresis techniques like Capillary electrophoresis, Gel permeation chromatography etc.

Tests for impurities

- Preparative liquid chromatography (LC)
- Liquid chromatography and ultraviolet detection (LC/UV)
- Liquid Chromatography and Mass Spectroscopy (LC/MS)
- Gas Chromatography (GC)
- Capillary Electrophoresis (CE)
- Supercritical Fluid Chromatography (SFC)
- Fourier Transform Infrared Spectroscopy (FTIR)

Liquid Chromatography and Ultraviolet detection (LC/UV)

Androstanolone

A sensitive, selective reverse phase method was developed for the quantitative determination of six potential impurities in Androstanol one active pharmaceutical ingredient. Efficient chromatographic separation was achieved on Zorbax Eclipse XDB C8 (250 × 4.6 mm, 5 µm) column with mobile phase containing a gradient mixture of solvent-A and solvent-B. The elucidated compounds were monitored at 200 nm. All six potential impurities were identified by mass spectrophotometer and characterized by nuclear magnetic resonance. The developed method was validated as per ICH guidelines with respect to specificity, precision, linearity, quantitative limit, detection limit and accuracy. Regression coefficient value was greater than 0.99 for Androstanol one impurities. Detection limit of impurity-A, impurity-B, impurity-C, impurity-D, impurity-E and impurity-F were in the range of 0.0002%-0.003% respectively. The quantitative limit of impurity-A, impurity-B, impurity-C, impurity-D, impurity-E and impurity-F were in the range of 0.003%-0.013% respectively with respect to sample concentration. The accuracy of the method was established based on the recovery obtained between 92.72%-106.90% for all impurities.

Hydrochlorothiazide and candesartan cilexetil

A simple, sensitive, and inexpensive high-performance liquid-chroma-to graphic method has been developed for simultaneous determination of hydro-chlorothiazide and candesartan cilexetil in pharmaceutical formulations. Chro-matographic separation was achieved on a Phenyl-2 column with a 25:75:0.2 mixture of 0.02 M potassium dihydrogen phosphate, methanol, and triethyl-amine, final pH 6.0 ± 0.1, as mobile phase. Detection was at 271 nm. Response was a linear function of concentration in the range 5–45 µg mL^{-1} for hydrochlorothiazide and 12–56 µg ml^{-1} for candesartan cilexetil; the correlation. Coefficients were 0.9993 and 0.9991, respectively. Total elucidate time for the two components was less than 5 min.

Metformin in plasma samples

A LC/MS method for the analysis of the highly polar anti-diabetic drug metformin in plasma samples is compared to an ion-pair HPLC method with UV detection. Both methods showed good linearity in the concentration range of 50 to 2000 ng/mL, good precision and accuracy and similar sensitivity. The LC-MS method has the advantage of a simpler and faster preparation procedure, shorter analytical times and higher selectivity. Both methods were validated and successfully applied to bioequivalence studies of drugs containing metformin.

Cetirizine

To develop and validate stability-indicating reversed phase high performance liquid chromatographic method for simultaneous determination of ketotifen fumarate and cetirizine dihydrochloride in solid dosage forms.

Caprolactum

A gas chromatographic technique has been developed for the determination of the impurities in caprolactam, using Carbowax 20 M as the partition liquid and Chromosorb P as the support, treated or untreated with potassium hydroxide. The system was used on a semipreparative scale for the separation of the two main impurities of ε-caprolactam, *viz*. 6-methyl-2-piperidone and octahydrophenazine, after enrichment by continuous crystallization. To confirm their identity, the two impurities were synthesized and injected into the gas chromatography. Other

impurities were identified by comparison of their retention times with those of known compounds. A technique was also developed to determine the degree of oxidation of caprolactam by gas chromatography.

Methanol and chloroform from liposomal

The use of liposomal formulations has rapidly gained popularity in pharmaceutical research and development. Their preparation often involves the use of organic solvents such as methanol and chloroform to dissolve lipophilic lipids. In the present study, gas chromatographic method for the determination of methanol and chloroform residual levels in liposomes was developed using GC 17 A Shimadzu with FID (a flame ionization detector) and the separation was carried out on BP 624 column (4% cyanopropyl phenyl and 94% dimethyl silixone, 30 m × 0.53 mm i.d. × 0.25 µm coating thickness), with nitrogen as a carrier gas in the split mode by direct injection method. The method was validated according to ICH guidelines. The method described is simple, sensitive, rugged, reliable and reproducible and requires less time than other reported methods for the quantitative of methanol and chloroform levels from liposomal formulations of lamivudine and stavudine.

Nitrogen trifluoride

Highly reactive fluorinated gaseous matrices require special equipment and techniques for the gas chromatographic analysis of trace impurities in these gases. The impurities that were analyzed at the low mg/L levels included dioxygen (O_2), dinitrogen (N_2), carbon dioxide (CO_2), carbon monoxide (CO), sulfur hexafluoride (SF6), methane (CH_4) and nitrous oxide (N_2O). Carbon tetrafluoride (CF_4) is also present in the product at levels of 20-400 mg/L and had to be analyzed as well. This paper compares the use of a custom-built dual-channel gas chromatograph utilizing single column back flush switching on one channel for the determination of O_2, N_2, CH_4 and CO with column sequence reversal on a second channel for the determination of CO_2, N_2O, SF_6 and CF4 to a similar system using a combination of dual-column back flush and heart-cut configurations. Pulsed discharge helium ionization detectors were used on both channels in both configurations.

Capillary Electrophoresis (CE)

The use of Capillary Electrophoresis (CE) to determine drug-related impurities is becoming established within industrial pharmaceutical analysis laboratories. Increasingly CE is being viewed as an alternative for, and complement to, High-Performance Liquid Chromatography (HPLC). This paper comprehensively reviews the progress of CE in drug impurity determinations subdividing the reports into low pH, high pH and MECC applications. The section covering method performance and validation clearly shows that CE methods are capable of validation in this area and can often give equivalent performance to HPLC methods. Possible benefits of adopting CE for this testing include reductions in costs and improved robustness. Potential developments are covered including the use of electrolyte additives, instrumental developments and the increased implementation of electro-chromatography. It is concluded that the current status of CE is sufficiently strong to allow the analyst to view CE as a viable and attractive alternative to HPLC.

Capillary Electrophoresis/Mass Spectrometry (CE/MS) is predominantly carried out using electrospray ionization (ESI). Recently, Atmospheric Pressure Chemical Ionization (APCI) and Atmospheric Pressure Photoionization (APPI)

have become available for CE/MS. With the VUV lamp turned off, the APPI source may also be used for CE/MS by Thermos Pray Ionization (TSI).

In the present study the suitability of ESI, APCI, APPI and TSI for drug impurity profiling by CE/MS in the positive ion mode is evaluated. The drugs carbachol, lidocaine and proguanil and their potential impurities were used as test compounds, representing different molecular polarities. A background electrolyte of 100 mM acetic acid (pH 4.5) provided baseline separation of nearly all impurities from the respective drugs. APPI yielded both even- and odd-electron ions, whereas the other ionization techniques produced even-electron ions only. In-source fragmentation was more pronounced with APCI and APPI than with ESI and TSI, which was most obvious for proguanil and its impurities. In general, ESI and TSI appeared the most efficient ionization techniques for impurities that are charged in solution achieving detection limits of 100 ng/mL (full-scan mode). APPI and APCI showed a lower efficiency, but allowed ionization of low and high polarity analytes, although quaternary ammonium compounds (e.g. carbachol) could not be detected. Largely neutral compounds, such as the lidocaine impurity 2,6-dimethylaniline, could not be detected by TSI, and yielded similar detection limits (500 ng/mL) for ESI, APPI and APCI.

In many cases, impurity detection at the 0.1% (w/w) level was possible when 1 mg/mL of parent drug was injected with at least one of the CE/MS systems. Overall, the tested CE/MS systems provide complementary information as illustrated by the detection and identification of an unknown impurity in carbachol.

Anti-cancer drug impurities

Due to the low therapeutic index of anti-cancer drugs, they should be closely monitored for evidence of potential contamination that may be of high toxicity and not to have the desired therapeutic effect. Therefore, analytical methods to detect drugs related substances at low concentrations are necessary. Capillary electrophoresis allows for fast and clear separation of drug derivatives. A multitude of sub methods make selection of suitable environment for various types of chemicals possible. Publications concerning separation of drugs such as cisplatin, carboplatin, lobaplatin, methotrexate, tamoxifen, paclitaxel from their derivatives, which are their potential contaminations, show that capillary electrophoresis provides the appropriate tools to analyze the impurities of these anti-cancer drugs and is able to partially displace such technique as thin layer chromatography and high performance liquid chromatography, which still play a major role in this field.

Ciprofloxacin

Capillary Zone Electrophoresis (CZE) has been elaborated for separation, identification and determination of ciprofloxacin and ‘its impurities. The separation, phosphate buffer pH 6.0 was supplemented with 0.075 M pentane- The elaborated method was validated. The selectivity, linearity, Limits of Detection (LOD) and quantification (LOQ), precision, and accuracy of capillary zone electrophoresis were evaluated. The results obtained by CZE were also compared with those obtained by liquid chromatography. Regarding the validation results the CE method fulfils the current European Pharmacopoeia requirements. The evaluated CE method could be applicable to the analysis of different medicinal products containing ciprofloxacin.

Retention mechanisms involved in Supercritical Fluid Chromatography (SFC) are influenced by interdependent parameters (temperature, pressure, Chemistry of the mobile phase, and nature of the stationary phase), a complexity which makes the selection of a proper stationary phase for a given separation a challenging step. For the first time in SFC studies, Parallel Factor Analysis (PARAFAC) was employed to evaluate the chromatographic behavior of eight different stationary phases in a wide range of chromatographic conditions (temperature, pressure, and gradient elution composition). Design of Experiment was used to optimize experiments involving 14 pharmaceutical compounds present in biological and/or environmental samples and with dissimilar physicochemical properties. The results showed the superiority of PARAFAC for the analysis of the three-way (column × drug × condition) data array over unfolding the multiway array to matrices and performing several classical principal component analyses [2].

Fourier Transform Infrared Spectroscopy (FTIR)

Antiparasitics: This study shows that Fourier Transform Infrared (FTIR) spectroscopy, Thermogravimetric Analysis (TGA), and Scanning Electron Microscopy (SEM) can be used as supporting tools for the evaluation of the quality of antiparasitic. In addition, an analytical methodology was developed and validated to quantify simultaneously Thiabendazole (TB), Febantel (FB), Toltrazuril (TZ), and Fluazuron (FZ) in bulk and in their veterinary pharmaceutical formulations using Reverse Phase High Performance Liquid Chromatography (RP-HPLC). In order to investigate stability, pharmaceuticals were submitted to degradation processes under different conditions, such as recommended by the International Conference on Harmonization. The chromatographic conditions were optimized and the validation parameters, such as selectivity, linearity, detection limit, quantification limit, precision, accuracy, and robustness showed results within acceptable standards. All analytes were stable in the stability assays in acid and basic media and thermal conditions, except in the oxidation process, which presented two degradation peaks. Physociochemical characterization by TGA, FTIR, and SEM of raw materials of TB, FB, TZ, and FZ provided information about the authenticity of the analytes, proving the wide applicability of the instrumental techniques. The RP-HPLC proposed method was found to be accurate, precise, and reproducible and can in addition be used for routine quality control analysis [3].

Simvastatin drug: In the present study a reversed phase high performance liquid chromatography (RP-HPLC) method with Diode Array Detector (DAD) at room temperature was used for obtaining impurity profiles of 20 drug products containing simvastatin as an active substance. Fourier-transform infrared spectroscopy (FT-IR) was carried out to obtain absorption spectra of samples. The Partial Least Squares (PLS) model was built to predict the relative content of lovastatin, the main impurity of simvastatin, and sum of statin-like impurities. In order to build the PLS model, peak areas obtained from HPLC chromatograms were related to FT-IR spectra of drugs. The PLS model based on signal normal variate and orthogonal signal correction (SNV+OSC) transformed FT-IR spectra was able to predict the content of drug impurities in real samples with a good prediction ability ($R2>0.95$).

Rosuvastatin: The objective of the present study was to develop Floating Drug Delivery System (FDDS) of rosuvastatin calcium is one method to accomplish tedious gastric residence times, provide convenience for both local and systemic drug action. Thus, gastro retention could help to provide higher availability of new products and

subsequently improved therapeutic activity and considerable benefits to patients. In this article aims at summarizing the floating drug delivery system along with types, access for designing the floating dosage form, advantages and disadvantages of FDDS. In this article, aims to maintain increasing floating retention time at the gastric site to reinforce the bioavailability and release rate of drug. The floating dosage form was processed by direct compression method adopting sodium bicarbonate as gas generating agent. The release rate was sustained up to 20 hrs with 1: 1.5 ratio of HPMC K4M and Xanthan gum, but the Floating Lag time was construct to be more with the combination. Evaluations of granules like physical parameters, weight variation, drug content uniformity, bulk density, tapped density, buoyancy studies, Swelling Index, angle of repose was done. Similarly, the aggregate between HPMC K4M and Guar gum also controlled the release more than 20 hrs was detected. The aggregate between HPMC K100 M and Carbopol 934P with the ratio of 2:1 was found to be acceptable with release profile. Hence the Formulation F10 was optimized by for further studies. The formulation (F10) also gratify the Swelling Index, Buoyancy time controlled the drug release up to 24 hrs. The mechanism of drug release pursued the Zero order kinetics with the co-efficient (R2) value 0.996.

Phenytoin Sodium (PS): Phenytoin Sodium (PS) has a tendency to convert to its base form; phenytoin base (PHT) during manufacturing, packaging, shelf life and in-use conditions that can influence its clinical performance. The objective of the present work was to develop a non-destructive, quick and easy analytical method for quantification of PHT in the drug product [4]. A formulation was prepared to contain the excipients of commercial capsule formulation of PS. The formulation containing either 100% PHT or PS was prepared and these formulations were mixed in different proportion to achieve 0%–100% PHT matrices. FTIR, NIR and Raman spectra of samples were collected. Data were truncated and mathematically pretreated before development of Partial Least Squares (PLS) and Principal Component Analysis (PCA) regressions model. The models were assessed by slope, intercept, R, R2, Root Mean Square Error (RMSE) and Standard Error (SEP). The models exhibited good linearity over the selected range of PHT in the formulations with low error as indicated by slope that was close to one and small values of intercept, RMSE and SE. The models of NIR based data were more accurate and precise than Roman data-based models as indicated by the low values of RMSE and SE. Prediction accuracy of independent samples containing 25% PHT using NIR models were similar to Roman models. On the other hand, the prediction was more precise for the independent sample containing 5% PHT using NIR data-based models compared to Roman data-based models as indicated by standard deviation (Table 2). In conclusion, chemometric models based on NIR and Roman spectroscopies provides a fast and easy way to monitor the disproportionation of PS in the drug products (Table 3) [5].

Table 2. Some examples of drugs and their impurities.

Drug	Impurity	Analytical method
Atropine sulphate	Apo atropine	Ultra violet spectroscopy
Cloxacillin	N, N dimethyl aniline	Gas chromatography

Dextrose	5-hydroxy methyl fulfural	Ultra violet spectroscopy
Diclofenac sodium	1-(2,6-dichlorophenyl) indolin -2-one	Liquid chromatography
Doxorubicin hydrochloride	Acetone and ethanol	Gas chromatography
Ethambutol hydrochloride	2–amino butanol	Thin layer chromatography
Framycetin sulphate	Neamycin	Ultra violet spectroscopy
Methamphetamine	1,2-dimethyl-3-phenylaziridine, ephedrine, methyl ephedrine, N formyl methamphetamine, Acetyl methamphetamine, N formylphedrine, Nacetyl ephedrine, N,Odiacetylephedrine,	Gas
	methametamine dimmer	chromatography

Table 3. Validation parameter for impurities present in drug substances.

Types of analytical procedure characteristic		Identification	Testing for impurities	
			Quantitative	Limit
Linearity		-	+	-
Range		-	+	-
Accuracy		-	+	-
Precision	Repeatability	-	+	-
	Intermediate	-	+(a)	-
Specificity(b)		+	+	+
Limit of Detection (LOD)		-	-(c)	+

Limit of Quantitation (LOD)	-	+	-

CONCLUSION

This review provides a perception on impurities in drug substance and drug products. Various regulatory authorities such as USFDA, MHRA, TGA and ICH already given emphasize in impurity profiling and governed such limit and regulation on this. So, it is very important to health care authorities give more attention on impurities present on drug product as because a little amount of impurities present in drug products can alter the biological as well as therapeutic efficacy. From the safety point of view also it is essential to do evaluation, isolation and detection of impurities. This article provides the important information about the impurities types, source and its classification, various techniques of isolation and characterization, analytical techniques for the determination, qualification of impurities and critical factors to be considered while preparation of the bulk drugs. Isolation and characterization of impurities is obligatory for acquiring and evaluating data that establishes biological safety which reveals the need and scope of impurity profiling of drugs in pharmaceuticals.

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