WWW.IJRPR.COM

International Journal of Research Publication and Reviews

Journal homepage: www.ijrpr.com ISSN 2582-7421

Advances in Impurity Profiling: A Comprehensive Review of Analytical Approaches and Regulatory Perspectives

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ABSTRACT :

Any organic material besides Active pharmaceutical ingredients API and of pharmaceutical elements is mentioned as impurity in the pharmaceutical sector that might flourish during formulation or originate on aging of APIs. These unwanted entities, even in small proportions, drives down efficacy and synergistically influence reliability of pharmaceuticals thus necessitates meticulous control, rigorous quantification, and thorough impurity profiling with validation. Impurities originate from distinct sources viz., reagents, heavy metals, ligands, catalysts, filter aids, starting materials along with intermediates and contaminants charcoal, residual solvents, by-products, degradation products. Extremally sophisticated instrumentation, viz., GC-MS, HPLC are pivotal in quantifying traces of drugs, impurities, and metabolites in distinct matrices. Degraded end products that originate during or after the bulk drugs manufacturing may contribute through enantiomeric impurities, hydrolysis, photolytic cleavage, oxidative degradation, along with decarboxylation. Limits for permissible impurity levels in APIs and formulations are being revised and adopted into pharmacopoeias more often. Current review explores the distinct types of impurities in APIs, their identifying approaches, and potential strategies to the disruptions they generate in pharmaceutical assessment.

Keywords: Impurities in pharmaceuticals, APIs, analytical identification approaches, sources of impurities, pharmacopoeial standards

1. Introduction :

Any element that coexists and inextricably entwin with the original drug is acknowledged as impurity encompassing starting elements, intermediates, and end products by virtue of adverse responses. (USP42, n.d.; Jorvekar & More, 2022) Its occurrence exceeding 0.1% ought to be revealed and quantified by virtue of selective analytical approaches. Proposed structures of impurities can be comprehended, that are earlier recognized through spectroscopic approaches acknowledge evidences for their identities and aids in optimizing reaction conditions and diminishing impurity to passable limits in final bulk drug formulations. Impurity profile is narration of both identified along with unidentified impurities exist in typical API batch fabricated through a meticulous process and is a pivotal aspect of contemporary industrial pharmaceutical analysis. International Conference on Harmonization (ICH) has put forward guidelines on impurities in new drug entities, products, and residual solvents, offering a framework to ascertain quality and safety of pharmaceuticals. (Görög, 2006)(Adhao & Thenge, 2020)

Impurity profiling (Bari et al., 2007a) acknowledged as analytical approaches emphasizing recognition, quantitatively addressing both organic along with inorganic impurities, and residual solvents, in bulk drugs and pharmaceuticals. ICH, US-FDA, and Canadian Drug and Health Agency are heavily emphasizing purity prerequisite and reorganization of impurities in APIs.

Impurity qualification emphasizes the significance of impurity profiling (Churi & Lokhande, 2017) in pharmaceutical sector by necessitating the gathering and assessment of data to demonstrate the biological safety associated with specific impurities. Guidelines Q3A(R2), 2006) in context of impurities in new drugs, products, and leftover solvents have been released by ICH. Supervisory agencies and pharmaceutical sector are heavily seeking impurity reference standards in addition to API reference standards. Estimation of impurity profiles in drug and allied entities has turn out as paramount area of focus in contemporary pharmaceutical analysis. Additionally, BP as well as USP are gradually integrating limits on permissible impurity levels in APIs along with pharmaceuticals.

3. Relevance of recognition of impurities (Q3A(R2), 2006) (Elemental impurity n.d.)

- Safeguard pharmaceuticals and accomplish patients' security
- Guarantee quality
- Pivotal in regulatory consent
- Affirms productiveness and stability
- Strategy optimization

Synthetic organic chemists typically either impede the manufacturing of a particular contaminant or conceptualize approach to purification to drive down its concentration to an acceptable threshold.(Dsouza et al., 2024) Once an Ineluctable impurity's structure has been figured it can be fabricated to offer enough stuff for:

- Final assertion of its structure
- Avail it as “impurity standard"
- Toxicological assessment (Emerce & Cok, 2012)

ICH Q3A guidelines enforced in context of drug, while (Q3B(R2), 2006) pertains to drug products and outline their indispensable assessment and documentation for investigating impurities as well as degradation products by virtue of stability assessment under apt storage requisites. Recognition of impurities below 0.1% is generally redundant unless impurities are ought to be unusually potent or toxic. Invariably, impurities ought to be qualified. Surplus assessment could be undertaken when there is no data to support the suggested specification level of impurity, in particular when conventional qualification threshold limits are surpassed.

Pursuant to ICH, maximum daily dose qualification threshold is as:

- For doses ≥ 2g/day: 0.05%.
- For doses ≤ 2g/day: 0.1% or 1 mg per day intake (whichever is lower)

1.2. Impurities that exist in pharmaceuticals are

- Activity-depressing
- Originate from colouring or flavouring entities
- Instituted owing to humidity
- Diminish shelf life
- Strike physical as well as chemical attributes
- Provoke incompatibility among entities.(Görög, 2006)

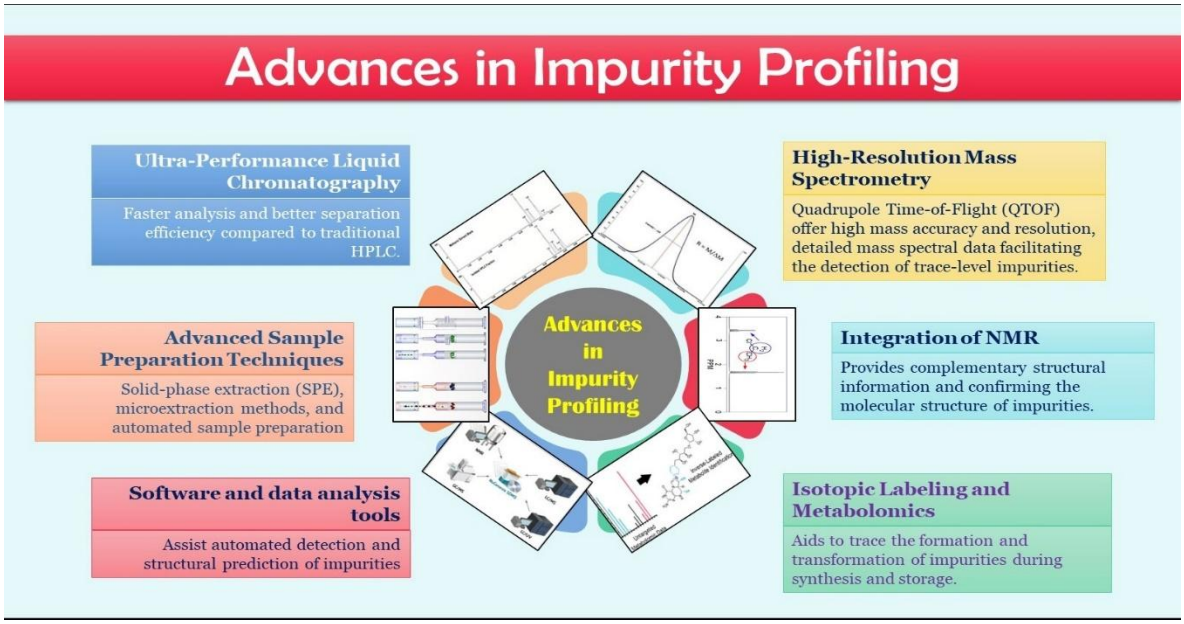

Figure 1: Advances in impurity profiling

2. Sorting of impurities :

Table 1: Sorting of impurity and its origin.(Dotzel, 2000) (Kumar Sharma, n.d.)

Impurity	Origin
Degraded drug product	Organic

Process-related drug product	Inorganic or organic
Process-related drug by products	Organic

2.1. Organic impurities (Step, n.d.) (Dattatraya et al., 2022)

Impurities that originate during fabrication and/or warehousing of pharmaceuticals, often acknowledged as degradants. Impurities entwined with synthetic strategy might originate from starting materials, intermediates, reagents, ligands, and catalysts employed in chemical synthesis, and from by-products or surplus reactions. Degradation impurities originate when the finished pharmaceuticals deteriorate chemically in fabrication or when it becomes subjected to suboptimal warehousing circumstances. (Richter et al., 2007)

These impurities ought to be identified, and might be volatile or non-volatile. Fabrication of chiral medicinal entities, encompass chiral impurities emergence and may coexist in finished pharmaceuticals. Whether in the feedstock, intermediate, or finished formulation, these impurities which might be with attenuated influential potential than API need to be treated or eradicated at distinct phases.

- **Starting materials** (Sources of Impurities, n.d.) **or intermediate impurities**. Although finished formulations are typically washed with solvents, unless manufacturers pay great attention to impede impurities, there remains a risk of leftover unreacted starting materials.
- **By-products**
  It rare to accomplish a single end product with complete yield in synthetic organic chemistry. By-products, which originate from unfinished or side reactions during synthesis, frequently coexist with the original product.
- **Degradation Products**
  Degradation of the finished formulation during the fabrication of bulk drugs might potentially result in impurities. This is usually brought on by inappropriate formulation storage circumstances, which over time could trigger the drug to drive down and deteriorate.

2.2. Inorganic Impurities (Kumar Shukla, 2014)

Metal and non-metallic inorganic impurities might be conveyed into the finished formulation as the consequence of the usage of distinct inorganic raw materials in fabrication. Table 1 presents sorting of the impurities. The emergence of inorganic impurities is aided by raw materials like acids, alkalis, alkaline earth metal compounds, reagents, catalysts, as well as inorganic salts. Water and metal catalysts utilized throughout drug production are principal origins of leftover metals and heavy metal impurities. These contaminants might originate from the leaching of process-related equipment such as centrifuges, dryers, transfer lines, reactors, along with micron filters. Although leftover metallic impurities are challenging to eradicate, they can be mitigated with the assistance of glass reactors along with distilled water. (Rawat et al., 2017)

a) **Reagents, Ligands, and Catalysts**: Although these impurities are relatively rare, their coexistence could originate from poor adherence to manufacturing processes, which might trigger consequences.
b) **Heavy Metals**: Heavy metals primarily occur in water, which are frequently employed in an array of manufacturing operations. This is especially so during acidification or acid hydrolysis. Glass-lined reactors as well as demineralized water are very effectual strategies to impede heavy metal contamination.
c) **Other Materials (Filter Aids, Charcoal)**: Filter aids that are frequently utilized in the fabrication of bulk drugs, including activated carbon and centrifuge bags, can also serve as origins for impurities. It is vital to periodically inspect bulk drug products for fibres and black particles so as to impede contamination.

2.3. Residual Solvents

Organic or inorganic liquids employed throughout manufacturing are often referred to as leftover solvents. It is often tough to eradicate these solvents throughout the working phase. To guarantee product safety as well as mitigate health perils, certain solvents that are known to be detrimental should be impeded while synthesizing bulk drugs.(Singh et al., 2024)

2.4. Formulation allied Impurities (R, 2024)(Rawat et al., 2017) (Ashlesha, 2022) (Arote et al., 2021) (Prabu et al., n.d.).

The inert substances employed in fabrication of the drug may contribute to the number of impurities in a drug product. The therapeutic element may be exposed to multiple circumstances throughout formulation, which could serve as region to degrade or cause other negative consequences.

In particular, solutions and suspensions are responsive to hydrolysis-induced deterioration. In addition to contributing impurities of its own, the water that serves in the formulation fosters a scenario that is conducive to hydrolysis and catalysis. Other solvents that serve the formulation process could experience comparable degradation processes.

Impurities in context of formulation can be sorted as follows, as depicted in Table 1.

- Method allied
- Environmental allied: Principal environmental attributes that can diminish stability
  a) Temperature
  b) Light-especially UV

c) Humidity

- Dosage form allied
  a) Interaction that exists between the components
  b) Functional group allied degradation
- Hydrolysis (Ester)
- Oxidative degeneration
- Photolytic spiting
- Decarboxylation

3. Typical keyword for impurities (Bari et al., 2007b) Q3C(R8), n.d.) (Tegeli et al., n.d.) (Rama Rao & Mani Kiran, n.d.)

3.1 Intermediate: Entities developed as an aspect of the synthesis operation or while the needed component is being synthesized.

3.2 Penultimate intermediate: The final molecule in synthesis chain that precedes final desired molecule that emerges.

3.3 By-products: Side reactions, encompassing incomplete, unfavourable and overreaction, degradation, rearrangement, or interactions entailing starting materials, intermediates, and chemical reagents or catalysts, may leave behind compounds that are not the intended intermediates and are acknowledged as side products.

3.4. Transformation products: These are pivotal subsets of impurities that originate from the chemical transformation of APIs and adjuvants or undergo chemical or physical alteration during their lifecycle, thus necessitating cautious identification and quantification that serve a paramount role in safety efficacy as well as regulatory compliance.

3.5. Interaction products: Intentional or inadvertent interactions between all the distinct chemicals utilized throughout the process yield these products.

3.6. Related products: These products might even be biologically active since they share chemical similarities with the pharmaceutical ingredient

3.7. Degradation Products: Products emerge as APIs or adjuvants of interest break down as a consequence of exposure to heat, light, and moisture.

4. Attributes influencing formulation associated impurities :

4.1. Environmental factors

i. **Exposure to adverse temperatures**: Potency may be lost, and impurities may accumulate in substances that are heat-sensitive or prone to deterioration in tropical conditions. For instance, heat-sensitive vitamins may degrade and depart from some of their nutritional value.(Zaiour et al., 2005)
ii. **Exposure to light:** When revealed to light, especially UV, photosensitive elements deteriorate, and impurities emerge.
iii. **Humidity:** Bulk powders as well as solid dosage forms are susceptible to humidity, directing the formation of impurities.

4.2. Impurity development with aging

Mutual interaction: Over time, impurity advancement may result from interactions among formulation components.

4.3. Impurities in context of Functional Group with examples

- **Ester Hydrolysis:** Aspirin, benzocaine, cefoxime, cocaine, and ethyl paraben.
- **Hydrolysis:** Benzyl penicillin, barbital, and chloramphenicol.
- **Oxidative Degradation:** Hydrocortisone, methotrexate, and API encompassing heterocyclic aromatic rings or nitroso/nitrile derivatives are responsive to oxidative degradation.
- **Photolytic Cleavage:** Products that are exposed to light throughout production and storage may generate impurities owing to photolytic cleavage.
- **Decarboxylation:** P-amino salicylic acid dissolved carboxylic acid that decarboxylates and releases impurities when heated since it loses CO_2.

5. Analytical method development (Rahman et al., 2006)

New drug development compels meticulous analytical data at distinct phases, encompassing:(Sapkal et al., 2023) (Bharti Mittu & Chauhan, 2015)

a) Choice of Sample Set

b) Screening of Chromatographic Conditions and Phases: executed by virtue of linear solvent strength model of gradient elution.(Johnson, n.d.; Rácz et al., 2018)

c) Method Optimization: entails fine-tuning parameters to guarantee ruggedness as well as robustness. (Siddhant Shelke et al., 2021) (Patil & S, 2009)

USP Signal-to-Noise Ratio (S/N)

S/N = 2 × height × scale to UV / peak-to-peak noise

Method for Establishing Exposure Limits: Residual Solvent Classes

- Class A: Solvents to be averted, recognized carcinogens.

- Class B: Solvents to be restricted owing to neurotoxicity or teratogenicity.(R Pounikar et al., 2020)
- Class C: Solvents with attenuated toxic potential.

Residual Solvent Limit computation (Class 3, 4):

Option 1: computed presuming 10 g oral dose: Concentration (ppm) = (1000 µg/mg) × PDE / dose

Option 2: By considering leftover solvent quantity.

Unless possible impurities are exceptionally hazardous or potent, it is not thought to be necessary to recognize them below 0.1% level. (<232> Elemental Impurities-Limits, n.d.)

Maximum Daily Dose Qualification Threshold

- For doses ≤ 2g/day: 0.1% or 1 mg/day intake (whichever is minimal).
- For doses > 2g/day: 0.05%.

6. regulatory guidelines pertaining to impurities (Lal et al., 2019)

1. ICH
    - Stability assessment of new drug substances and products - Q1A
    - Impurities within New Drug Substances - Q3A
    - Impurities in New Drug Products - Q3B
    - Impurities: Guidelines for leftover solvents - Q3C
2. US-FDA
    - NDAs -Impurities in New Drug Substances
    - ANDAs – Impurities in New Drug Substances
3. Therapeutic Governance Authority (TGA), Australia

In conformity with the ICH, regulatory authorities were consulted throughout the development of this guideline by ICH expertise working group.

7. Characterization approaches (Görög, Babjak, et al, 1997) (Skrdla, Abrahim, et al, 2006) (ICH, 2005).

GC-MS, HPLC demonstrates pivotal role in recognizing minor entities, entailing drugs, impurities, degradation products, and metabolites, in district matrices. (Jangala et al., 2014) (Saibaba et al., n.d.)

7.1. Nuclear Magnetic Resonance: Offers insights of stereochemistry as well as bonding structure of molecules, thus rendering it indispensable tool for pharmaceutical analysis's structural clarification. (Mistry et al., 1999a) (Mohapatra & Griffin, n.d.) (Fulmer et al., n.d.)

7.2. MS: Over the past few decades, MS has fostered a significant role in pharmaceuticals. Innovations in interface efficiency and design have render it practicable to integrate separation strategies like GC and HPLC with ease. This opened up new avenues for drug-related element monitoring, assessment, and quantification in APIs and finished formulations.(Armirotti et al., 2007) (Rao et al., 2021)

8. Isolation strategies (Zawilla et al., 2007) (Mistry et al., 1999b)

Sophisticated instrumental techniques are implemented, the impurities are directly characterized in addition to isolation by virtue of chromatographic and non-chromatographic strategies employed to isolate impurities prior to characterization. Chromatographic reactor denotes usage of analytical-scale column as both flow-through reactor and a separation medium for reactants and products. E.g., HPLC chromatographic reactor approach, solution-phase hydrolysis kinetics of Aprepitant (Emend™) prodrug, fosaprepitant dimeglumine, were investigated. Impurities like ofloratidine in loratidine, as well as impurities in drugs like celecoxib and amikacin, are typical examples.

Strategies for isolating impurities (Kumar et al., 2016)

1.Extraction
    - Solid-phase
    - Liquid-liquid
    - Accelerated solvent
    - Supercritical fluid

2.Column chromatography
    - Flash
    - Thin Layer
    - Gas

3.HPLC (Kamani & Sujatha, 2022)

4.High-Performance Thin Layer Chromatography

5.Capillary Electrophoresis

6.Supercritical Fluid Chromatography

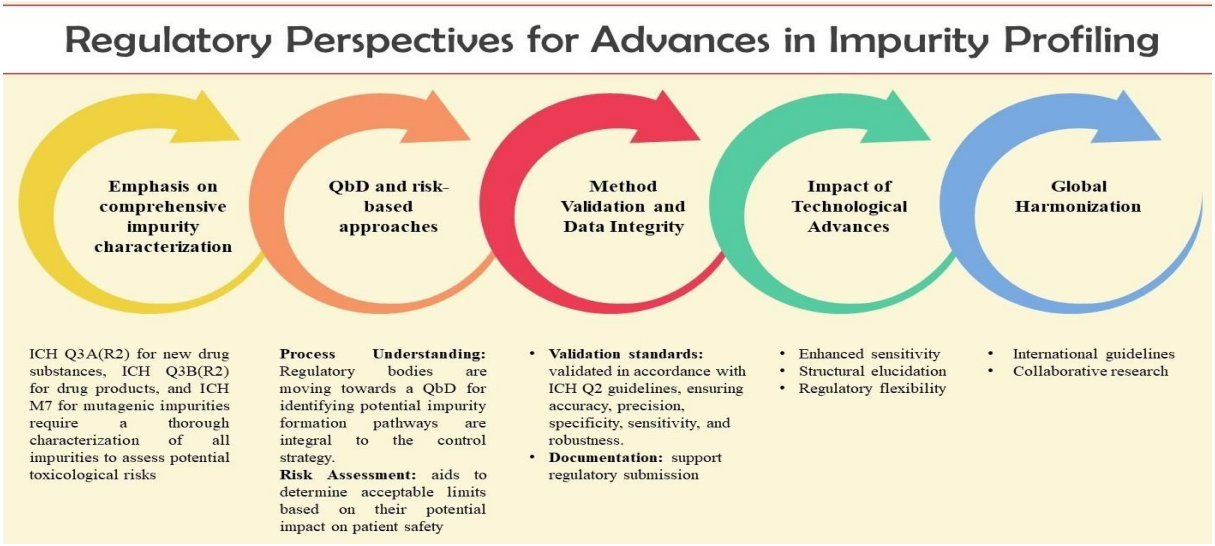

Figure 2: Regulatory perspectives for advances in impurity profiling(Gogna, 2020)

9. Conclusion :

Current review comprehends perspective on impurities in drug as well as drug products. As drug safety acquires more attention in the literature, the impurity profile of pharmaceuticals growing more and more relevant. The article offers valuable insights of sorting of impurities, isolation and characterization strategies, analytical approaches for determining as well as qualifying impurities. It also emphasizes critical factors in context of fabrication of bulk drugs. Pharmacopoeia compelled to recognize and quantify impurities exist in APIs and finished formulations. Impurity profiling serves as pivotal quality control means and offers toxicity as well as safety, detection limits, quantification limits for both organic and inorganic impurities in APIs and finished formulations. Regarding these impurities, unique specifications and standards are desperately needed.

10. REFERENCES :

1. <232> Elemental Impurities-Limits. (n.d.).
2. USP42. (n.d.).
3. Adhao, V. S., & Thenge, R. R. (2020). Elemental Impurities: A Review. 17–21. www.stmjournals.com
4. Armirotti, A., Millo, E., & Damonte, G. (2007). How to Discriminate Between Leucine and Isoleucine by Low Energy ESI-TRAP MSn. Journal of the American Society for Mass Spectrometry, 18(1), 57–63. https://doi.org/10.1016/j.jasms.2006.08.011
5. Arote, S., Dhamak, K. B., & Bhangale, C. J. (2021). An overview on impurity profiling of drug and pharmaceutical formulations. www.ijcrt.org
6. Ashlesha, B. B. (2022). Impurity Profiling: A Review. Asian Journal of Pharmaceutical Research and Development, 10(2), 135–143. https://doi.org/10.22270/ajprd.v10i21052
7. Bari, S., Bari, S. B., Kadam, B. R., Jaiswal, Y. S., & Shirkhedkar, A. A. (2007a). Impurity profile: Significance in Active Pharmaceutical Ingredient. Eurasian Journal of Analytical Chemistry, 2(1). https://www.researchgate.net/publication/215866887
8. Bari, S., Bari, S. B., Kadam, B. R., Jaiswal, Y. S., & Shirkhedkar, A. A. (2007b). Impurity profile: Significance in Active Pharmaceutical Ingredient. Eurasian Journal of Analytical Chemistry, 2(1). https://www.researchgate.net/publication/215866887
9. Bharti Mittu, A. C., & Chauhan, P. (2015). Analytical Method Development and Validation: A Concise Review. Journal of Analytical & Bioanalytical Techniques, 06(01). https://doi.org/10.4172/2155-9872.1000233
10. Churi, S. K., & Lokhande, M. V. (2017). Impurity Profiling of Pharmaceutical Drugs By Various Methods. IOSR Journal of Applied Chemistry, 10(07), 27–34. https://doi.org/10.9790/5736-1007012734
11. Dattatraya, J. P., Priyanka Dattatraya, J., Shete, M., Arun, N., Deshmukh, V. K., Ghawate4, V. B., & Pund, A. R. (2022). A review on nitrosamine impurities present in drugs. In Pharmaceutical Resonance (Vol. 4, Issue 2).
12. Dotzel, M. M. (2000). / Notices VII. Submission Requirements department of health and human services Food and Drug Administration International Conference on Harmonisation; Draft Revised Guidance on Impurities in New Drug Substances. In Federal Register (Vol. 65, Issue 140). http://www.fda.gov/cber/
13. Dsouza, S. J., Sandeep, D., Charyulu, R. N., Gowrav, M., & Pradeep, H. (2024). Impurities in Drug Substance-An Overview of ICH Q3A, Q3C and M7 Guidelines. International Journal of Pharmaceutical Investigation, 14(2), 299–305. https://doi.org/10.5530/ijpi.14.2.37
14. Elemental impurity analysis in regulated pharmaceutical laboratories. (n.d.).

15. Emerce, E., & Cok, I. (2012). Overview of impurities in pharmaceuticals: Toxicological aspects. In Asian Chemistry Letters (Vol. 16, Issue 1). https://www.researchgate.net/publication/259150621
16. Fulmer, G. R., Miller, A. J. M., Sherden, N. H., Gottlieb, H. E., Nudelman, A., Stoltz, B. M., Bercaw, J. E., & Goldberg, K. I. (n.d.). Supporting Information NMR Chemical Shifts of Trace Impurities: Common Laboratory Solvents, Organics, and Gases in Deuterated Solvents Relevant to the Organometallic Chemist.
17. Gogna, K. (2020). Regulatory aspects of Impurity profiling. International Journal of Drug Regulatory Affairs, 8(4), 45–54. https://doi.org/10.22270/ijdra.v8i4.433
18. Görög, S. (2006). The importance and the challenges of impurity profiling in modern pharmaceutical analysis. In TrAC - Trends in Analytical Chemistry (Vol. 25, Issue 8, pp. 755–757). https://doi.org/10.1016/j.trac.2006.05.011
19. International conference on harmonisation of technical requirements for registration of pharmaceuticals for human use ich harmonised tripartite guideline impurities in new drug products Q3B(R2). (2006).
20. INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE ICH HARMONISED TRIPARTITE GUIDELINE IMPURITIES IN NEW DRUG SUBSTANCES Q3A(R2). (2006).
21. International council for harmonisation of technical requirements for pharmaceuticals for human use impurities: guideline for residual solvents Q3C(R8). (n.d.).
22. Jangala, H., Vats, P., Khuroo, A. H., & Monif, T. (2014). Development and Validation of a LC-MS/MS Method for the Simultaneous Estimation of Amlodipine and Valsartan in Human Plasma: Application to a Bioequivalence Study. In Scientia Pharmaceutica (Vol. 82, Issue 3, pp. 585–600). Osterreichische Apotheker-Verlagsgesellschaft m.b.H. https://doi.org/10.3797/scipharm.1402-11
23. Johnson. (n.d.). 4 Column characterization and selection doravisky.
24. Jorvekar, A. R., & More, V. S. (2022). Impurity Profiling and Degradation Study: A Review. IJRAR22B2476 International Journal of Research and Analytical Reviews. www.ijrar.org
25. Kamani, V. G., & Sujatha, M. (2022). An innovative stability indicating hplc method with impurity profiling of niraparib-an anticancer drug in pharmaceutical formulations. Rasayan Journal of Chemistry, 15(4), 2976–2983. https://doi.org/10.31788/RJC.2022.1546590
26. Kumar, N., Devineni, S. R., Singh, G., Kadirappa, A., Dubey, S. K., & Kumar, P. (2016). Identification, isolation and characterization of potential process-related impurity and its degradation product in vildagliptin. Journal of Pharmaceutical and Biomedical Analysis, 119, 114–121. https://doi.org/10.1016/j.jpba.2015.11.044
27. Kumar Sharma, S. (n.d.). Sources And Types of Impurities. https://www.researchgate.net/publication/387559663
28. Kumar Shukla, P. (2014). Handbook of Inorganic Impurities in Pharmaceuticals. https://www.researchgate.net/publication/280224434
29. Lal, B., Kapoor, D., & Jaimini, M. (2019). A review on analytical method validation and its regulatory perspectives. Journal of Drug Delivery and Therapeutics, 9(2), 501–506. https://doi.org/10.22270/jddt.v9i2.2403
30. Mistry, N., Ismail, I. M., Farrant, R. D., Liu, M., Nicholson, J. K., & Lindon, J. C. (1999a). Impurity profiling in bulk pharmaceutical batches using 19 F NMR spectroscopy and distinction between monomeric and dimeric impurities by NMR-based diffusion measurements. In Journal of Pharmaceutical and Biomedical Analysis (Vol. 19).
31. Mistry, N., Ismail, I. M., Farrant, R. D., Liu, M., Nicholson, J. K., & Lindon, J. C. (1999b). Impurity profiling in bulk pharmaceutical batches using 19 F NMR spectroscopy and distinction between monomeric and dimeric impurities by NMR-based diffusion measurements. In Journal of Pharmaceutical and Biomedical Analysis (Vol. 19).
32. Mohapatra, S., & Griffin, D. (n.d.). AI-assisted reaction impurity prediction and inverse structure elucidation.
33. Patil, J. S., & S, P. J. (2009). Optimization techniques: An introductory overview. Journal of Pharmacy Research, 2(2). https://www.researchgate.net/publication/38111481
34. Prabu, S. L., Lakshmana Prabu, S., & Suriyaprakash, T. N. K. (n.d.). Impurities and its importance in pharmacy. In International Journal of Pharmaceutical Sciences Review and Research (Vol. 3, Issue 2). www.globalresearchonline.net
35. R, B. (2024). Recent Approaches of Impurity Profiling in Pharmaceutical Analysis: A Concise Review. Medicinal & Analytical Chemistry International Journal, 8(1), 1–14. https://doi.org/10.23880/macij-16000191
36. R POUNIKAR, A., J UMEKAR, M., & R GUPTA, K. (2020). Genotoxic impurities: an important regulatory aspect. Asian Journal of Pharmaceutical and Clinical Research, 10–25. https://doi.org/10.22159/ajpcr.2020.v13i6.37370
37. Rácz, N., Molnár, I., Zöldhegyi, A., Rieger, H. J., & Kormány, R. (2018). Simultaneous optimization of mobile phase composition and pH using retention modeling and experimental design. Journal of Pharmaceutical and Biomedical Analysis, 160, 336–343. https://doi.org/10.1016/j.jpba.2018.07.054
38. Rahman, N., Azmi, S. N. H., & Wu, H. F. (2006). The importance of impurity analysis in pharmaceutical products: An integrated approach. Accreditation and Quality Assurance, 11(1–2), 69–74. https://doi.org/10.1007/s00769-006-0095-y
39. Rama Rao, N., & Mani Kiran, S. S. (n.d.). Pharmaceutical Impurities: An Overview. In Indian Journal of Pharmaceutical Education and Research (Vol. 44, Issue 3).
40. Rao, R. R., Kumar, G. R., Vardhan, V. M., & Boddu, V. (2021). A Simple and Sensitive LC-MS/MS Method for Determination and Quantification of Potential Genotoxic Impurities in the Vismodegib Active Pharmaceutical Ingredient. Journal of Pharmaceutical Research International, 88–102. https://doi.org/10.9734/jpri/2021/v33i44b32654
41. Rawat, S., Kumar, V., & Healthcare, H. (2017). Impurity profiling: overview on impurity profiling and reporting methodologies adopted by united states and europe. Rawat et al. World Journal of Pharmaceutical Research, 6, 206. https://doi.org/10.20959/wjpr201714-9863
42. Richter, J., Jirman, J., Havlíček, J., & Hrdina, R. (2007). Pioglitazone impurities. Pharmazie, 62(8), 580–584. https://doi.org/10.1691/ph.2007.8.6720

43. Saibaba, S. V, Kumar, M. S., & Ramu, B. (n.d.). Pharmaceutical impurities and their characterization: a review. www.ejpmr.com
44. Sapkal, D. B., Shinde, G. M., Charde, M. S., Chakole, R. D., & Doijad, R. M. (2023). Bioanalytical method development and validation: a review. In International Journal of Creative Research Thoughts (Vol. 11, Issue 6). www.ijcrt.orgwww.ijcrt.orgc378
45. Siddhant Shelke, M., Santosh Waghmare, M., & Kamble, H. (2021). A review on optimization techniques in pharmaceutical formulation. www.ijcrt.org
46. Singh, K., B, K. S., & C, B. K. (2024). Pharmaceutical impurities: a multifaceted review of origins, classification, analysis and control. In Certified Journal │ Kavya et al. European Journal of Pharmaceutical and Medical Research (Vol. 11). www.ejpmr.com
47. Sources of Impurities in Pharmaceuticals. (n.d.).
48. Step. (n.d.). The European Agency for the Evaluation of Medicinal Products Human Medicines Evaluation Unit ICH Topic Q 3 A Impurities Testing Guideline: Impurities in New Drug Substances Note for guidance on impurities testing: impurities in new drug substances (CPMP/ICH/142/95). http://www.eudra.org/emea.htmlCPMP/ICH/142/95
49. Tegeli, V. S., Gajeli, G. B., Chougule, G. K., Thorat, Y. S., Shivsharan, U. S., & Kumbhar, S. T. (n.d.). International journal of drug formulation and research significance of impurity profiling: a review. 2. www.ordonearresearchlibrary.org
50. Zaiour, A., Hamdoun, B., Charara, J., Roumi, M., Zahraman, K., & Hage-Ali, M. (2005). A New Theoretical Formulation of Temperature Effect on Impurities Diffusion Coefficients in Molten Tellurium. Physica Scripta, 71(4), 414–418. https://doi.org/10.1238/physica.regular.071a00414
51. Zawilla, N. H., Li, B., Hoogmartens, J., & Adams, E. (2007). Improved reversed-phase liquid chromatographic method combined with pulsed electrochemical detection for the analysis of amikacin. Journal of Pharmaceutical and Biomedical Analysis, 43(1), 168–173. https://doi.org/10.1016/j.jpba.2006.06.043