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Impurities in drug substances and drug products: A risk-based approach

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This article is the second in a series focused on regulatory management of impurities in drug substances and drug products from a regulatory chemistry, manufacturing, and controls (CMC) perspective. The first article examines the main international guidelines related to impurities, and this article outlines a risk-based approach for regulatory management of impurities. Upcoming articles will present simulated case studies for impurities management in drug substances and drug products.

Keywords – CMC, ICH, impurities, regulatory, strategy

Introduction

The first article in this series discusses the main international guidelines related to impurities, with a specific focus on mutagenic, nitrosamine, and elemental impurities.[1] Knowing the technical and regulatory theory underlying impurity management is important, but even more critical is understanding how the theory applies in practice. What to investigate, when, with what level of detail, and how to document everything while maintaining an approach aligned and compliant with regulatory guidelines and the expectations of the competent authorities are issues that all companies face when they are developing or registering a medicinal product.

This article discusses the concept of a risk-based approach for impurities management during the product lifecycle, from development to marketing authorization.

Development phases

The drug product and drug substance formulation, manufacturing process, and analytical development phases are critical steps for regulatory CMC. Several aspects may contribute to uncertainty during development: a lack of technical knowledge and experience with the molecule, frequent CMC changes to

improve synthesis, process, and analytical methods, and potential ambiguity in the regulatory guidelines. Considering these uncertainties, it is important to pinpoint what must be accomplished at each development stage and how CMC changes applied during development, including the evolution of the drug substance and drug product quality profile, should be justified. CMC changes during development are inevitable, and regulatory authorities require the demonstration of quality consistency throughout each step, from early development phases up to registration for approval and into lifecycle maintenance.

Impurities assessment

From the impurities management perspective, the degree of rigor associated with impurity investigations is often dictated by the phase of development of the project. In-depth investigations are not usually necessary to ensure safety with regard to impurities during early clinical trials;[2] during later phases of development, in-depth studies are performed to determine the origin and fate of impurities.

Theoretical prediction of impurity formation can be beneficial and may help the company to manage unexpected issues during development.

A preliminary risk assessment should be carried out to identify and evaluate all potential impurities at the drug substance and drug product level. The investigation should focus on chemical properties of the materials used in the manufacturing process as well as any other components that may come in contact with the product during production and storage.

Preliminary risk assessments for potential impurities should be conducted for both the drug substance and drug product. At the drug substance level, a preliminary risk assessment should consider the chemical properties of the molecules involved in the synthesis and that side chemical reactions may occur, with correlated likelihood for each potential impurity. At the drug product level, preliminary risk assessments should evaluate compatibility with excipients, considering the chemical properties of both the drug substance and excipients, as well as compatibility with other components that may come in contact with the product during process and storage. The risk assessment should be followed by appropriately designed experimental studies.

A stepwise risk-assessment approach for impurities evaluation is an important part of regulatory management, not only during development but also in the postapproval phase. A stepwise approach includes:

- Identification of all possible sources of impurities;
- For each possible source, definition of the necessary actions to determine if and which impurities may derive from that specific source; and
- Implementation of control strategies to mitigate the impurity-related risk.

A risk assessment should involve the product in its entirety, from the drug substance to the finished product, so that a certain impurity can be managed from the beginning, ensuring a better-quality production lifecycle.

Identification of impurities

The step of identifying all potential impurities may be considered the most important aspect of the process. If the risks are not identified, analyzed, and evaluated properly, decisions about how to control risk cannot be made efficiently. There are several tools to identify risk, such as fishbone diagrams, process mapping, and process breakdown, and various tools and methodologies to analyze the risks. The most important aspect is the composition of the teams assessing the risk, which should include not only representation from regulatory affairs but also technical experts from research and development, quality, and manufacturing departments.

Cross-functional teams significantly reduce the risk of overlooking any sources of impurities. In cases where it is reasonable to suppose that a given impurity may negatively impact the patient's health, as may be the case for genotoxic impurities, the involvement of toxicologists and clinical experts should also be considered.

Knowledge and analysis of manufacturing processes are essential aspects of determining sources of impurities. In particular for drug substances, the manufacturing process is the main potential source of impurities: numerous steps of chemical synthesis, possibility of side reactions and relative formation of by-products, the use of solvents and catalysts, and extreme reaction conditions, such as very acidic or very basic pH or high reaction temperatures, are factors that increase the risk of having impurities in the drug substance. For a drug product, the study of its degradation assumes greater importance: stability and forced degradation studies are very useful in defining the impurity profile of the drug product. Useful information can also be obtained from suppliers, for example, by studying in detail the specifications and the production process of the starting materials and excipients.

Risk elimination and reduction

Identifying the sources of potential impurities and determining which impurities are present in the product are necessary but not sufficient steps by themselves. Adequate risk elimination and risk reduction measures should be considered. Theoretically, the best approach would be to eliminate the source of the impurity, but that is not always possible. Lack of chemical synthesis alternatives, lack of alternative suppliers of starting materials and excipients, difficulties in modifying manufacturing processes and reaction conditions can make it difficult to eliminate a given impurity and its source. The most probable scenario is to define actions aimed at reducing the levels of each impurity, and therefore the risks, as much as possible. These actions must be evaluated considering the

specific phase of the project (e.g., clinical Phase 1, clinical Phase 2), the controls already in place, the actual opportunities for modifying or improving the manufacturing process and the analytical procedures, and clinical aspects of the product, such as dosage and medical target population. Doing so helps assess the situation with respect to the amount of effort required to eliminate or reduce the level of impurity.

Documentation and strategy

Risk assessments should be regarded as living documents. It is also a good practice to establish dedicated risk assessments per risk, for example, individual assessments for risks associated with elemental impurities or nitrosamines. Maintaining updated risk assessments ensures better regulatory oversight and helps identify the best management strategies. For example, in the early stages of clinical development, rigorous control of some categories of impurities may not be required, such as in the case of elemental impurities, but as the development project progresses, control of elemental impurities becomes necessary.

According to the ICH Q3D guideline,[3] control of elemental impurities is not mandatory for drug products used during clinical research stages of development, but it is mandatory for the registration step. Furthermore, as the clinical and development process progresses, regulatory authorities may request preliminary information on elemental impurities management. It is therefore important to evaluate and document risk from the outset of the process and to have a strategy in place to ensure product quality.

Conclusion

Having a CMC regulatory strategy for managing impurities is not just about identifying what is applicable at a given stage of development and implementing the requirements of a guideline. A successful CMC regulatory strategy embraces a wide-ranging vision that can focus on the most critical impurities in a specific stage of development while also defining actions to monitor the aspects that will become fundamental in a later stage.

The levels of impurities in pharmaceutical products and their regulatory management is an important challenge that companies and regulatory bodies must navigate. Pharmaceutical companies need regulatory strategies that allow continuous management of impurities from the development phase to the postmarket phase. A risk-based approach offers companies a tool for managing impurities throughout the product lifecycle.

Abbreviations

CMC, chemistry, manufacturing, and controls; **ICH,** International Council for Harmonisation

About the author

Yuri Ceragioli, MS, is a senior regulatory affairs associate at Parexel. He has more than eight years' experience in regulatory affairs of healthcare products, with a focus on CMC aspects of small molecules. Ceragioli has a bachelor's degree in molecular and industrial biotechnology from the University of Pisa (Italy) and master of science degree in regulatory affairs from the University of Parma (Italy). He can be reached at Yuri.Ceragioli@parexel.com

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Reference list

All references were checked and verified on 18 December 2023.

1. Ceragioli Y. Impurities in drug substances and drug products: A regulatory CMC perspective. Regulatory Focus. Published online xx December 2023. https://www.raps.org/News-and-Articles/News-Articles/2023/12/Impurities-in-drug-substances-and-drug-products-A
2. Alsante KM, et al. Recent trends in product development and regulatory issues on impurities in active pharmaceutical ingredient (API) and drug products. Part 1: Predicting degradation related impurities and impurity considerations for pharmaceutical dosage forms. AAPS PharmSciTech. Published 27 November 2013. Accessed 17 February 2023. https://doi.org/10.1208/s12249-013-0047-x
3. International Council for Harmonisation. Guideline for elemental impurities Q3D(R2). Adopted 26 April 2022. Accessed 22 June 2023. https://database.ich.org/sites/default/files/Q3D-R2_Guideline_Step4_2022_0308.pdf