The relevance of chemistry, manufacturing and controls (CMC) in drug development

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Introduction

Drug development is a multidisciplinary process that is initiated once a pharmacological target is identified and lead compounds are selected from drug discovery. Selection of the lead compound is followed by the generation of data from multiple scientific disciplines. Non-clinical studies — such as pharmacodynamics, pharmacokinetics, drug metabolism, and toxicology— are conducted in parallel **with CMC-related activities** to ensure that the lead compound is suitable for clinical evaluation.

CMC activities are **fundamental aspects of early drug development**. Although its significance is often underestimated, it plays a critical role in ensuring that the development of a lead compound is not only effective but also safe, stable, and consistently produced.

CMC activities integrate the principles of drug formulation, manufacturing processes, and quality control, all of which are critical for transitioning a lead drug candidate from laboratory research through the various clinical phases and ultimately to the market.

CMC planning and risk factors identification: the importance of early-development focus

- During **early phases of drug development**, **long-term planning** is essential. Therefore, CMC planning and risk factors identification should begin at early stages, well **in advance of the late non-clinical or clinical phases** to mitigate potential risks timely, and to prevent costly issues that could jeopardize clinical trials or delay marketing authorisation approvals.

- To mitigate risks, it is critical to establish **a well-defined CMC strategy** that includes **risk management evaluation at every development stage.** This involves conducting thorough testing and maintaining flexibility to address unforeseen challenges throughout the process.

- A clear understanding of, and **compliance with regulatory requirements** (e.g. EMA, FDA, ICH) from the outset is **crucial. Regulatory alignment across the CMC development** process helps avoid delays, rejections, or clinical holds in the clinical phases that could significantly **impact the timely delivery** of medicinal products to **the market**.

- Early **interactions with regulatory bodies** through available procedures (Scientific Advice, pre-IND and end-of-phase 2 meetings among others) provide invaluable guidance during drug development to ensure that medicinal products are aligned with the regulatory expectations.

Key elements of a general CMC development plan

Drug substance characterisation

Characterisation of the active pharmaceutical ingredient (API) regarding solubility, solid state properties (potential polymorphism, particle morphology and particle size distribution); understanding the chemical structure, purity and potential degradation pathways (including the evaluation of mutagenic impurities) and stability, for **chemical compounds** is crucial. **For biologics**, it is relevant the characterisation of biologic structure such as protein sequence, peptide mapping, protein folding, charge heterogeneity, and post translational modifications. Additionally, it includes the screening for or engineering out of specific regions for degradation or undesired modifications.

Setting of Critical Quality Attributes (CQA)

CQAs for a given product should be set early in development prospectively based on the **quality target product profile of the product**, on the API properties and should be progressively refined as additional product knowledge is gained over time.

Formulation development

The development of a robust, scalable, and effective formulation is vital for advancing the lead drug candidate into clinical phases. Factors such as the choice of excipients, route of administration and the dosage form are driven by the API's properties.

Manufacturing Process Development

The manufacturing process is intended to consistently produce the formulated drug in sufficient quantities and optimising the conditions under which the drug product is manufactured to ensure scalability, reproducibility, and cost-effectiveness. It is **relevant** to use **Quality by Design tools** to link CQAs to critical process parameters to anticipate and prevent variations in product quality. This is particularly essential for biologics and complex molecules, as minor variations in process parameters can significantly affect product quality.

Transitioning from laboratory-scale production to full-scale manufacturing involves new challenges: ensuring process reproducibility, optimising equipment and meeting increased **production demands**. **Scale-up planning activities** focus on evaluating the feasibility of **replicating the manufacturing process at a larger scale** with no impact on the **manufacturing process robustness**.

Analytical method development

Analytical methods are developed to assess the **quality and consistency** of the **developed drug product** throughout the various phases of development. These methods must be validated according to the requirements defined at each stage of development.

Stability

Stability studies provide **information** on the **physical, chemical**, and **microbiological attributes** of formulated drug products. Potential degradation pathways are anticipated in the evaluation of products subject to temperature, humidity, light, and pH variations. The information obtained enables to **identify and mitigate stability-related issues** early in the development process.

Conclusion

The complexity and importance of CMC considerations in pharmaceutical development cannot be underestimated.

Early CMC planning and risk identification during the drug development process are crucial to mitigating potential issues that could not only increase development costs, but also delay timely market access for the medicinal product.

Awareness of and compliance with regulatory requirements from the earliest stages, and throughout the development pathway, will contribute to the delivery of a high-quality, safe and effective medicinal product.

Guidelines Overview

The following list, while not exhaustive, highlights relevant regulatory frameworks from ICH, EMA, and FDA.

- ICH Q11 (2012) Development and manufacturing of drug substances (chemical entities and biotechnological/biological entities)
- ICH Q8 (R2) (2009) Pharmaceutical Development
- ICH Q9 (2005) Quality Risk Management
- ICH Q10 (2008) Pharmaceutical Quality Systems
- ICH M7 Assessment and control of DNA reactive (mutagenic) impurities in pharmaceuticals to limit potential carcinogenic risk
- Draft ICH Q1 guideline on stability testing of drug substances and drug products (EMA/CHMP/ICH/130561/2025)
- Guideline on the requirements to the chemical and pharmaceutical quality documentation concerning investigational medicinal products in clinical trials (EMA/CHMP/QWP/545525/2017 Rev. 2)
- Guideline on the requirements for quality documentation concerning biological investigational medicinal products in clinical trials (EMA/CHMP/BWP/534898/2008 Rev. 2).
- Guideline on the Development and Manufacture of Synthetic Peptides (EMA/CHMP/CVMP/QWP/387541/2023)
- FDA Guidance for Industry: Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs, Including Well Characterized, Therapeutic, Biotechnology-derived Products
- FDA Guidance for Industry: INDs for Phase 2 and Phase 3 Studies: Chemistry, Manufacturing, and Controls Information

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