SAFC®
Pharma & Biopharma Raw Material Solutions

White Paper

Navigating The Regulatory Maze: Fundamentals for Drug Development

Navigating through the evolving regulatory landscape can be a challenge, especially for early-stage biotechnology companies developing a drug for the first time. The production process developed for new drug candidates is governed by a stringent and extensive set of requirements to which every manufacturer must adhere. Understanding and properly applying these regulations are critical to success and avoiding unnecessary delays. Even if the choice is to outsource development and manufacturing, knowledge of fundamental regulatory terminology is invaluable as the potential new drug advances towards commercialization or possible acquisition by a pharmaceutical partner.

This primer offers a description of some key regulatory concepts and highlights the Emprove® program, that has been designed to help accelerate and reduce risk throughout the drug development journey.

GMP vs non-GMP: What is the Difference?

Good Manufacturing Practice (GMP) is a set of processes, procedures and documentation requirements for that the International Council for Harmonization provides a widely acknowledged framework and is legally implemented in various countries by the respective responsible authorities. GMP describes the minimum standard that pharmaceutical manufacturers must meet to ensure their products are consistently produced and controlled according to established quality standards for many aspects including record keeping, personnel qualifications, sanitation, cleanliness, equipment qualification and process validation. Adherence to GMP -among other things- helps minimize the risk of errors and contamination. GMP requirements are relatively general and allow manufacturers to decide how to best implement the necessary controls. While this offers a good deal of flexibility, it requires that the manufacturer carefully and properly interprets the requirements.

Raw and starting materials are included in GMP requirements for drug production and can be a source of confusion, especially as some materials used in biopharmaceutical production processes are also available in non-GMP forms. A simple example is sodium chloride; the same chemical composition is available in both GMP and non-GMP grades such as that used in food applications. Non-pharmaceutical GMP sodium chloride may contain caking additives, which are usually unwanted and inappropriate in pharmaceutical-grade GMP material.

Whenever a material of appropriate GMP is available, authorities expect that it will be applied in pharmaceutical production. Traceable and comprehensive documentation is standard for GMP materials and an appropriate quality agreement should be available; in contrast, this documentation can be quite limited for non-GMP material.

If a change in the manufacturing process of a critical non-GMP material occurs, there is a need to evaluate the impact regarding human use. GMP material regulations provide guidance as to when an impurity must be listed and the process must be appropriately validated to reduce process variation. Insufficient change management for non-GMP grade materials can create a significant risk for patient safety. It is also important to keep in mind that the use of a non-GMP material would require additional control steps in the manufacturing process and a complex justification in the drug registration procedure.

GLP: What does it mean?

Good Laboratory Practice (GLP) is a quality system concerned with the organizational process and conditions under which non-clinical health and environmental safety studies are planned, performed, monitored, recorded, archived, and reported. This definition has been applied in member states of the Organization for Economic Cooperation and Development (OECD) and has been implemented in the countries by corresponding laws such as EU Directive 2004/10/EC or 21 CFR 58 in the US.

GLP principles, in their strict regulatory sense, apply only to studies on pharmaceuticals which are non-clinical. These studies are mostly conducted in animals or *in vitro*, include analytical aspects, and are performed to obtain data on the properties and/or safety with respect to human health and/or the environment of the tested substances. Results of these studies are intended to be submitted to a national registration authority for the purposes of registering or licensing the tested substance or any product derived from it.

GMP: A Sliding Scale

For drugs used in clinical trials, appropriate GMP requirements are expected. GMP is a "sliding scale”; during the development of the drug manufacturing process, different standards and requirements are applied for different clinical phases. By the time a product reaches Phase 3 clinical trials, GMPs are expected to be fully followed during manufacturing. Chapter 19 of the ICH Good Manufacturing Practice for Active Pharmaceutical Ingredients provides detailed information about GMP requirements for APIs for use in clinical trials. In chapter two, quality is defined by the appropriate GMP concept that requires evaluation of process and quality problems.

Supplier support for the pharmaceutical producer is critical. Information provided by the supplier about their applied quality system may help to define the appropriate GMP adopted for the status of development.

During early development, process validation is normally not applicable where a single API batch is produced or where process changes make batch replication difficult or inexact. The combination of controls, calibration and where appropriate, equipment qualification, must assure API quality during this phase. Process validation should be conducted in accordance with the validation requirements described in section 12 of the ICH Q7 Good Manufacturing Practice. When batches are produced for commercial use, even if at pilot or small scale, changes are expected as knowledge is gained, and production is scaled up. Every change in the production, specifications, or test procedures should be adequately recorded, notified to and approved by the competent authority, if required. Raw material change information from suppliers may be integrated in a quality agreement with the supplier; this can help reduce the impact of unintended changes to the final product.

Documentation of API manufacturing and access to raw material information from suppliers can also help optimize development steps and support risk assessment activities. The supplier can enrich the knowledge of the pharmaceutical producer to optimize the development testing and control strategy by providing a range of information including:

- The quality system of the supplied materials
- Release testing methods
- The validation approach of the manufacturing
- Change notification commitments
- Information about the applied testing methods and the release control and shelf life information

ICH Q7: A Reference in Quality System Standard

ICH Q7 Good Manufacturing Practice for Active Pharmaceutical Ingredients, the most commonly referenced quality system standard in pharmaceutical production, contains five segments:

- General requirements for the applied quality system
- Production, which includes in-process control and raw material changes
- Control, which governs the need for laboratory control, validation, and change control
- External contacts, which addresses supply chain topics and contract manufacturing
- Specific topics defining requirements for APIs produced by fermentation and requirements for cell cultures and APIs used in clinical trials

Chapter 19 of the ICH Q7 guide defines that controls used in the manufacture of APIs for use in clinical trials should be consistent with the stage of development and appropriate GMP concepts should be applied. This approach reflects that requirements may change with the development of the manufacturing process.

The pharmaceutical manufacturing process is complex with a great deal of risk. The ICH Q9 Quality Risk Assessment is used as an established standard for detecting and mitigating risk of pharmaceutical production. To perform a successful risk assessment as outlined in ICH Q9, the manufacturing process must be evaluated in detail, including raw materials. Traceable information about the raw and starting materials used in the manufacturing is essential during this evaluation. Access to this information during the early stages of development may significantly reduce later stage risks.

The following information about raw and starting materials used in production represents an appropriate starting point for a robust risk assessment of their possible impact to the drug:

- Original manufacturer
- Validation of the release testing of the raw materials
- Shelf life of the material
- Impurities
- Ability of the supplier to inform about changes and sign a QA agreement
- Availability of information throughout the shelf life of the material

With a comprehensive set of documentation, assessment of the impact on raw material changes on reproducibility will be facilitated.

Resources

Developing and manufacturing biopharmaceuticals is a complex process requiring management of multiple suppliers and many raw materials within an evolving regulatory landscape. We offer the Emprove® Program to help manufacturers minimize disruptions and conduct thorough risk assessments when moving from development to manufacturing.

The Emprove® Program provides raw and starting materials that are stringently qualified according to industry-leading standards. These products are supported by comprehensive online documentation packages that meet pharmaceutical manufacturers' information needs when qualifying raw materials, completing a risk assessment, and optimizing a manufacturing process. The program contains more than 400 raw and starting materials, 20 filter and single-use product families, as well as a growing portfolio and cell culture media and chromatography resins. The products are supported with Emprove® Dossiers which provide comprehensive, up-to-date documentation to aid in navigating regulatory challenges, managing risks, and improving manufacturing processes.

To learn more:

- Read our white paper: Identifying Appropriate-Quality Raw Materials in an Evolving Regulatory Environment
- Visit our website: **Sigmaaldrich.com/emprove**

Merck KGaA
Frankfurter Strasse 250
64293 Darmstadt, Germany

To place an order or receive technical assistance

Please visit: **MerckMillipore.com/contactPS**

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