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## Manufacturing Scale-Up of Drugs and Biologics

Refer to the **NIH SEED Regulatory Knowledge Guides** for more specific guidance on the regulation of:

- Small Molecule Therapeutics
- Biological Products

### Context

The U.S. Food and Drug Administration (FDA) requires innovators to ensure the quality and safety of new drugs and document each stage of their manufacturing processes as they move from the laboratory to pilot scale, to clinical scale, and eventually to commercial scale manufacturing. During pilot scale manufacturing, innovators must develop a chemistry manufacturing and controls (CMC) plan that describes the sequential and parallel activities that are involved in optimizing and scaling-up drug manufacturing. The CMC plan includes a [quality management system](#) to ensure compliance with FDA requirements. Once the early development work is complete and the product quality and safety have been demonstrated, innovators scale-up manufacturing to provide sufficient drug product to support clinical trials, and if needed, retain samples for bridging studies. Ramping up to commercial scale manufacturing requires attention to many details to ensure both process stability and product integrity.

### Key Differences in Manufacturing Drugs and Biologics

The manufacturing processes for small molecule therapeutics, referred to as “drugs,” and biologics – much larger and complex molecules – are fundamentally different. Drugs are synthesized through chemical processes. This form of manufacturing, known as chemical synthesis, involves the sequential combination of chemicals in a controlled environment. These drugs possess well-defined structures, enabling complete analysis to identify all components within the final pharmaceutical product. This method ensures that each batch of the drug produced is consistent with its predecessors.

Biologics present a stark contrast in their manufacturing. They are not chemically synthesized but are cultivated within living systems such as microorganisms or plant or animal cells. This biological process inherently leads to batch-to-batch variability, so while each dose meets stringent quality standards, it’s normal for them to have minor differences. Biologics, and similarly biosimilars, can be vastly more complex than small molecule drugs, sometimes by an order of magnitude of 1,000 times in size, and are produced through specialized, proprietary biological processes.

Drugs generally require fewer critical process steps than biologics, which undergo numerous essential stages of their synthesis and production. The scale-up from laboratory to commercial production for biologics is a delicate operation that demands substantial investment and a high degree of precision – any error could result in significant setbacks or complete failure. As noted in the [Regulatory Knowledge Guide for Biological Products](#), “the process is the product” and any changes in the manufacturing process can result in a fundamental change to the biological molecule, impacting the product and its performance, safety, or efficacy.

Despite these differences in manufacturing, the following content is relevant for developers of both drugs and biological products.

### Scale-Up Process

The transition from laboratory to commercial scale is a multistep endeavor that requires meticulous planning and execution.

#### Process Development versus Scale-Up

- **Process Development:** This stage is focused on crafting and refining the production process, exploring various methods, adjusting parameters, and monitoring outcomes to establish the most efficient production method.
- **Scale-Up:** The scale-up process involves increasing the production volume, often translating a bench-scale process to an industrial-scale operation.

#### Stages of Scale-Up

- **Laboratory Scale:** Initial development and testing occur on a small scale, allowing for process tweaking without the risks and costs associated with larger scales.
- **Pilot Scale:** This intermediary stage is crucial for fine-tuning the production process in a near-real-world environment to anticipate and rectify potential issues. The steps in the process (a.k.a. unit operations) are defined and ideally locked.
- **Commercial Scale:** The definitive stage where production is ramped up to meet commercial demands. Process stability is critical at this juncture as changes can significantly impact costs and product integrity – unit operations are not changed except to accommodate increased scale.

### Regulatory Compliance and Practices

Manufacturers in the pharmaceutical industry must adhere to strict regulations imposed by authorities such as FDA and the European Medicines Agency (EMA) in the European Union. These regulations meticulously oversee the entire manufacturing lifecycle, encompassing every step from the procurement of raw materials to the final stages of product packaging. The primary goal is guaranteeing pharmaceutical products’ safety, efficacy, and quality.

#### Early Development and Research Use Only (RUO) Documentation

In the nascent stages of drug development, documentation is tailored for RUO. This includes a general identification of raw materials, process durations, yields, and other preliminary data. Adherence to Good Manufacturing Practices (GMP) is not obligatory. RUO environments offer a degree of latitude,

permitting developers to experiment and refine their processes without the stringent constraints imposed by GMP regulations.

#### Transition to IND-Enabling Documentation

As the product advances toward the Investigational New Drug (IND) application stage, the documentation must evolve to become more granular. This encompasses details such as the identities of manufacturers, lot numbers, preparation dates of reagents, exact process timings, in-process controls, and monitoring protocols. The shift towards more stringent process controls is crucial for ensuring product consistency and reliability, paving the way for human clinical trials. GMP standards take precedence at this stage, necessitating comprehensive records of all materials and processes to meet the regulatory criteria for producing clinical trial or commercial material.

#### Clinical Trials and GMP Compliance

Upon entering clinical trials, using GMP-compliant materials becomes imperative to ensure safe administration to humans. This phase is characterized by thorough process validation, aseptic processing, and strict adherence to quality control measures. These practices are vital for preserving the product's integrity and safety for human use.

#### Quality Control and Regulatory Standards

Both drugs and biologics are held to exacting quality control standards, mandated to comply with the regulatory frameworks enforced by FDA and EMA. This entails extensive testing to confirm that the product meets all safety and efficacy benchmarks at each scale-up phase. While the "10X rule" suggests that a batch size can be increased tenfold without significant alterations, this principle is not universally applicable due to the complexities of scaling up. Considerations such as raw material quality, cost-effectiveness, and product integrity are paramount.

#### Documentation and Batch Records

As developers gain deeper insights into their products, the documentation process becomes more dynamic. Maintaining batch records allows comparison of current production lots with previous ones, establishing the definitive characteristics of the finished product. This ongoing documentation is essential to ensure that any modifications in the manufacturing process do not detrimentally impact the product's quality, safety, or efficacy.

#### Evaluating Consistency: Comparability and Bridging Studies

It may be necessary to implement changes to the manufacturing process throughout the clinical development lifecycle and even after a product has received approval. Regulatory agencies must execute comparability studies to ensure these changes do not compromise the product's established quality, safety, and efficacy.

The core aim of comparability studies is twofold:

- Process Evaluation – These studies scrutinize any alterations in manufacturing procedures, equipment, or sites to confirm the production remains under stringent control and the resulting product aligns with the pre-established quality benchmarks.

- Product Assessment – Post-process modifications, the studies rigorously examine the end product to verify its physical, chemical, biological, and microbiological attributes are consistent with the original product specifications.

Comparability studies become particularly critical under circumstances such as:

- Production Scale-Up – When increasing the production volume.
- Site Transference – When shifting manufacturing operations between facilities.
- Component and Equipment Modifications – When changing essential manufacturing components or machinery.

### Methodology of Studies

These evaluations typically encompass analytical testing and might extend to nonclinical and clinical assessments to affirm that the new manufacturing process is equivalent to the established one. Should the modified product be similar but not identical to the original, bridging studies are mandated to validate the new product's equivalence regarding human interaction compared to the existing data.

### Importance of Comparability Studies

Fundamentally, comparability studies are a suite of rigorous evaluations demonstrating that the product's therapeutic efficacy and safety profile remains intact despite any process alterations. They are indispensable in upholding pharmaceutical products' consistent quality and efficacy throughout their market life.

### Bridging Studies for Product Alterations

When modifications lead to a product that is similar but not identical to the original, bridging studies are imperative. These studies are pivotal in demonstrating that the alterations have not significantly influenced the product's interaction with humans, as corroborated by pre-existing data. The specific requirements for these studies can differ based on the regulatory jurisdiction and the nature of the product, underscoring the importance of continuous engagement with regulatory authorities during the development and scale-up phases.

### Conclusion

Understanding the distinct roles and applications of GMP and non-GMP manufacturing is crucial within the pharmaceutical industry. Manufacturers must navigate the complex regulatory landscape to ensure their products consistently meet the highest safety, efficacy, and quality standards. The meticulous manufacturing and scale-up processes in pharmaceutical production reflect the industry's unwavering dedication to upholding stringent standards throughout a drug or biological product's lifecycle.

### Regulatory Resources:

- [Developing and Manufacturing Drugs Including Biologics](#)
- [Biologics Guidances](#)
- [How Do Drugs and Biologics Differ?](#)
- [Pilot-Scale Studies, Scaling-Up, and Technology Transfer](#)

- [Five Factors to Consider When Scaling Up Biologics Production to Meet Global Commercial Output](#)
- [A Quick-Start Guide to Biologics Manufacturing](#)
- [Q5E Comparability of Biotechnological/Biological Products](#)
- [Q5E Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process](#)
- [Manufacturing Changes & Comparability for Human Cellular & Gene Therapy Products](#)
- [Manufacturing Process of Biologics](#)
- [A Survey of FDA Approved Monoclonal Antibodies and Fc-fusion Proteins for Manufacturing Changes & Comparability Assessment](#)
- [Biopharmaceutical Manufacturing: The Challenge of Global Regulatory Compliance](#)
- [Guideline on Comparability after a Change in the Manufacturing Process – Non-Clinical & Clinical Issues](#)
- [RUO to GMP—Considerations for Biotech Companies](#)
- [Comparability Protocols for Human Drugs and Biologics: Chemistry, Manufacturing, and Controls Information Guidance for Industry](#)
- [ICH Q5E Comparability of Biotechnological/Biological Products](#)
- [Manufacturing Changes and Comparability for Human Cellular and Gene Therapy Products](#)
- [Question and Answers: Comparability Considerations for Advanced Therapy Medicinal Products](#)