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Regulatory Knowledge Guide for Biological Products

NIH SEED Innovator Support Team

Introduction

Drugs—molecules which are intended to diagnose, cure, mitigate, treat, or prevent disease—are regulated by the **U.S. Food and Drug Administration** (FDA). The FDA regulates the manufacture and marketing of both small molecule and biologic drugs.

This guide focuses specifically on the development of biologic drug products. These include therapeutic proteins, monoclonal antibodies, and vaccines. Biological drugs are made from living organisms and vary in product complexity, manufacturing processes, and end-user application. For biologic products that modify genetic material to improve function or fight disease, please refer to the Regulatory Knowledge Guide for Cell and Gene Therapies.

The regulatory paths for biologics and small molecule drugs have some similarities and significant differences. This guide refers to the Regulatory Knowledge Guide for Small Molecules in sections where the processes are the same, so it is essential that you also familiarize yourself with the Small Molecules guide for those topics. This guide explicitly outlines key areas where biologic drug development is different from small molecule drug development. In addition, the resource sections for this guide complement the resources provided in the small molecules guide, so please refer to both resource sections as needed.

For biologics, it is critical to remember that the process is the product. Any changes in manufacturing can fundamentally change the biologic molecule and impact its efficacy. Therefore, as part of the regulatory process a manufacturer must assure FDA of its ability to provide a product of consistent quality and purity by defining the parameters and control points in its manufacturing processes.

For biologics, "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.

Biologics are regulated by both the Center for Biologics Evaluation and Research (CBER) and the Center for Drug Evaluation and Research (CDER) at FDA.

- CDER regulates the less complex biologics—such as monoclonal antibodies, peptides, and hormone protein products.
- CBER regulates the more complex biologics—such as vaccines and blood products.

Throughout the product development process, seek feedback on your research and development plans through formal and informal meetings with FDA. The first step in evaluating a new biologic drug is to file an **Investigational New Drug** (IND) application with FDA. This is updated regularly with safety information, clinical protocols and supporting documents, manufacturing information, and other data. Eventually—if all goes according to plan—the IND information supports a **Biologics License Application** (BLA). Information about IND requirements and exemptions can be found in Guidance for Clinical Investigators, Sponsors, and IRBs.

Link to Vaccine Regulatory Case Study

Please use the Word navigation panel to jump to relevant sections for your specific needs. Bolded terms within the text are defined in the Glossary.

If you have questions about the biologics drug development process, contact the SEED Innovator Support Team or FDA.

After reading this Regulatory Knowledge Guide, you will have a better understanding of biological **drug product** (DP) development and the regulatory lifecycle. Specific topics that will be described include:

- How to create a preliminary **target product profil**e (TPP) for the biological product to guide your development strategy.
- Best practices for developing robust analytical assays that are critical to establish **drug substance** (DS) and DP quality attributes for comparability and product release.
- Why the performance and consistency of the biological product is highly sensitive to the quality and suitability of starting materials and the manufacturing process.
- When to meet with FDA and why it's important to have a clear understanding of the regulatory requirements of the proposed development pathway early in the process.
- How to plan IND-enabling animal studies that will demonstrate the safety and efficacy of the DP prior to the first-in-human clinical trial.
- The role of immunogenicity testing and why it's required for regulatory approval of biologics.
- Why product development and phase-appropriate manufacturing processes need to achieve suitable product quality and safety profiles for Phase I investigational drugs.
- How a phase-appropriate **quality management system** (QMS) in alignment with FDA regulations can support **chemistry manufacturing control** (CMC) elements.
- How to ensure that the manufacturer is a good fit for the DP being developed.

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1 Defining the Biological Drug Candidate

Refer to Section 1 of the Regulatory Knowledge Guide for Small Molecules because of the high-level similarities in this step. The basic pathway for drug development is the small molecule pathway, as described in the small molecule guide. While biologics share many of the development and regulatory approaches of small molecules, the focus of this guide is on the divergences between these two types of drugs. Throughout this guide, you will be referred to the Small Molecules Guide as appropriate, for information that is common with biological products.

There are many characteristics to consider in the time between first observing a "druggable" condition and deciding if or how to move forward with a biologic drug development program – one where the **bulk drug substance** (BDS) is a biological ingredient. Vital considerations include the ability of a biological molecule to change a disease state, as well as your ability to measure the degree of that effect and deliver that molecule to its functional space in the human body. It is best to start the development process with a vision of the final product. Developing a **Target Product Profile** (TPP) early will help guide the research and decision-making process (see Section 1.3 for a full discussion of TPPs and the monoclonal antibody [A-Mab] and vaccine [A-VAX] case studies for examples).

Early development of a TPP will provide a vision to guide your research and decision-making process.

Most biological products are derived from natural biological/cell-based sources or living organisms or tissues. They are large complex polydisperse molecules compared to synthesized small molecule drugs. Biologics exist as viscous fluids, solutions, and suspensions. They are often more challenging to manufacture (produced in smaller yields after multistep process/unit operations) and characterize (batch-to-batch equivalence, identity, and purity must be maintained) because of the inherent variations resulting from even minor changes in the manufacturing process. It is anticipated that slight differences between manufactured lots of the same biological product (i.e., acceptable within-product variations) are typical and expected.

Biologics are susceptible to degradation due to shear forces, shipping, freeze/thaw cycles, temperature changes, exposure to oxygen and light, physical stress, excipient interactions, container storage, etc. The structural and physicochemical properties of the **biological product** can influence formulation, scale-up, and manufacturability processes (expression and harvest yield titers, stability of the biologic in expressed form, etc.), which can affect its potency and biological performance (safety and efficacy).

Before selecting an optimal biologic product, multiple *in vitro* assays demonstrating the product's suitability, identity, potency, purity, and stability are continuously optimized throughout pre-market development. FDA assesses the manufacturing process and the manufacturer's strategy to control the biologic product within-product variations as part of its review. These control strategies are put in place to help ensure that manufacturers produce biological products with consistent clinical performance.

1.1 Target Identification (Indication/ Disease/Pathway)

You may conduct many experiments without a target, but it is unlikely that you can accomplish any actual product development work until the target is defined. Adopting a TPP (see example TPPs for a biological product and a vaccine) can help mitigate this risk. Alternatively, a Compound Profile Table—as developed by the Blueprint network for small molecule evaluation—can be adapted and modified for biologics development in very early-stage efforts.

As is the case with small molecule drugs (see Section 1 of the Regulatory Knowledge Guide for Small Molecules), FDA pays particular attention to the target **indication**/disease/pathway of a specific lead biologic and the characterization of the underlying molecular mechanism by which the biologic works. When investigating the properties of a suitable target you may consider the following:

- Confirmed role in the pathophysiology of a disease and/or confirmation as disease-modifying
- Accessibility, expression, and concentration levels that are detectable for the biological product
- Whether expression is or is not evenly distributed throughout the body
- 3D structure availability to assess druggability
- Ease or difficulty in assaying and enabling high-throughput screening
- A promising toxicity profile, with potential adverse effects that are predictable using phenotypic data
- Favorable intellectual property (IP) status (relevant for pharma companies)

The following lists available methods to address the problem of target identification (a.k.a. deconvolution) and highlights recent advances. Findings from multiple approaches are typically used to confirm the target.

Approaches for Identifying and Validating the Target and Understanding the Biological Product's Molecular Mechanism

- **Transcriptional, genomics, and proteomics profiling**
- **Discovery of genes that may encode immunogenic antigens and proteins, proteins that may show aberrant expression patterns in disease states, target sequence diversity, and identify antigens containing conserved and variable immunological domains**
- **Data mining using bioinformatics**
- **Identifying, selecting, and prioritizing potential disease targets**
- **Genetic association**
- **Genetic polymorphism and connection with the disease**
- **Expression profile**
- **Functional analysis and changes in mRNA/protein levels (overexpression, transgenics, antisense RNA, gene variants)**
- **Pathway and phenotypic analysis**
- ***In vitro* cell-based mechanistic studies and cell-based models**
- **Functional screening**
- **Knockdown, knockout, or using target-specific tools**
- **Analysis of signaling pathways**
- **Protein interactions (pull-down assays, yeast two hybrid)**

1.2. Identification of Lead Biologic Product

Identifying lead biologic product candidates requires product screening campaigns. The campaigns seek to screen and optimize candidates by ranking and selection based on selectivity, binding, affinity, and kinetics (from very fast on rates to very slow off rates). Standard approaches may involve data mining and multiple assay platforms, including virtual, biochemical, biophysical, cell, and phenotypic-based screening. A "manufacturability" or "developability" assessment should be performed on identified lead biologics that specifically considers the expression level in the host cell, route of administration, formulation, stability requirements (especially aggregation), product- and process-related impurities, and sequence liabilities (especially post-translational modifications). ***In silico*** immunogenicity prediction to minimize **anti-drug antibodies** (ADAs) is also helpful. Together, this information helps ensure that issues of development and manufacturing are accounted for during the discovery phase and the lead candidate best matches the vision you described in your TPP.

1.3. TPP for Biologics

A TPP outlines the desired "profile" or characteristics of a target product that is aimed at a particular disease or diseases. TPPs state intended use, target populations and other desired attributes of products, including quality, safety, and efficacy-related requirements. The complexity and heterogeneity of biologics compared to small molecules require more emphasis on the quality requirements. Refer to Sections 1 and 2 of the Regulatory Knowledge Guide for Small Molecules for a discussion of the key concepts that also apply to biologics.

The biopharmaceutical development and manufacturing strategies for biologic products are guided by the product's TPP. The TPP defines the product and development targets and is intended to ensure that the product is designed to meet patient needs and efficacy requirements. The TPP is a table that outlines the characteristics of the drug in key categories such as: therapeutic area, indication, patient population, efficacy, safety, dosage regimen, route of administration, formulation, and **active pharmaceutical ingredients** (APIs). As new information becomes available throughout product development, it is used to iteratively update the TPP—a point of emphasis for biologics is on refining structure-function relationships and their impact on safety and efficacy. Two industry- and regulatory-led case studies (A-Mab and A-VAX) for developing and manufacturing biological products are available, including example TPPs.

Resources:
Article: A–Mab: A Case Study in Bioprocess Development
Article: A-VAX: Applying Quality by Design to Vaccines

1.4. Druggability Optimization

Druggability refers to the capacity of a drug to reach and bind to its intracellular or extracellular target with sufficient affinity to modulate or disrupt the target's activity. Optimizing the druggability of biologics to be effective in desired clinical patient populations requires knowledge of the biologic candidate's desired TPP and *in vivo* performance/attributes. Please read Section 2.1 of the Regulatory Knowledge Guide for Small Molecules for an in-depth description of actions to take to identify and optimize druggable qualities.

During a development program, the biologic product's ability to interact with its target will need to be optimized using multiple assays—from acellular to cellular models, and in both small and large animals—before being tested in humans. Some biological systems work in concert, using multiple proteins and factors to elicit a

biological activity. If you are targeting such a system, you need to ensure your models include all known components of the binding/activity complex to guide optimization.

The use of **artificial intelligence** (AI) and **machine learning** tools and methods for druggability optimization is highly encouraged. For biologics, AI increasingly delivers value using multiomics to inform precision targeting, generation and optimization of clinical candidates, and clinical-trial optimization based on predictions of the best therapy using patient samples.

Resources:
Article: Genetic-Driven Druggable Target Identification and Validation
Article: Panomics for Precision Medicine
Article: Inverse Pharmacology: Approaches and Tools for Introducing Druggability into Engineered Proteins
Article: Applications of Machine Learning in Drug Discovery and Development
Tool: FTMap

1.5 Validation Through Proof-of-Concept Pharmacological Testing

As the biologic molecule is identified and the development effort expands, the evaluation of activity and other key characteristics must become both more robust and more diverse. This will support your continued development of a more refined TPP. A high-quality, regularly updated TPP provides an opportunity to identify, describe, and resolve misalignments that can doom the product. It is also a powerful communication document when approaching and reporting to investors. Are the drug development assumptions still valid? Is there new scientific data that impacts drug development plans? Has the competitive landscape changed? These are important questions, and the TPP is an indispensable tool to grapple with them.

A clearly defined strong biologic lead with **pharmacodynamic** endpoints will set the stage for strong indicators of efficacy at the appropriate decision point. At this stage of development, however, there is not yet enough information about the biologic's efficacy, safety, **toxicity**, **pharmacokinetics**, and metabolism in animals and humans. See Section 2 of the Regulatory Knowledge Guide for Small Molecules for additional information.

Resource:
EMA: ICH Topic Q 6B: Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products

1.6 Demonstrating Bioactivity

For small molecule drugs, the dose is defined by the amount of the drug administered (determined by weight). By contrast, biologics are dosed based on a range of specific activity determined using a functional bioassay. Given the complexity and heterogeneity of biologics, defining the potency of the biologic is essential. Bioassays (called potency assays) are biochemical and cellular assays that validate the proposed mechanism of action of a new drug. Potency assays ideally demonstrate an effect on the target disease, although this is relatively rare as surrogate indicators are often employed. Robust potency assays are also used during in-process and release testing. The kind of bioassays developed will depend on the therapeutic modality, product class, and attributes unique to the biologic molecule.

Functional Bioassay Requirements

- **Reliably reproduce results**
- **Define/predict binding to the target system**
- **Modulate the target and associated cellular pathways**
- **Illustrate the mechanism of action**
- **Indicate potential cytotoxicity**
- **Predict clinical correlation**

Resources:
FDA: How Should I Measure This? An FDA perspective on the Bioanalytical Method Validation
FDA: Points to Consider in the Manufacture and Testing of Monoclonal Antibody Products for Human Use
EMA: ICH Topic Q 6B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products

2 Early Manufacturing Requirements

Refer to Section 3 of the Regulatory Knowledge Guide for Small Molecules for a discussion of the key concepts that apply to biological products. Also, see Appendix A for a high-level biologics manufacturing process flow diagram.

What's the difference between a small molecule and a biologic? Besides size, the critical difference between these two therapeutic types is that small molecule drugs are chemically derived, while biologics are extracted from living organisms. Most drugs today are small molecule compounds manufactured by chemical synthesis. But as our understanding of disease processes increases, we also see biological product candidates, including antibodies, interleukins, and vaccines. Both drug types involve comprehensive and expensive development prior to Market Authorization, but the translational pathways also differ.

Because of these differences, this section has several subsections that differ from the corresponding section in the small molecule guidance.

In the case of biologics, the process defines the product: variation in biologics is usually influenced by the manufacturing processes, which adds complexity to the development. Developability and scalability of the manufacturing process are more challenging than for small molecules because the manufacture of the DS in cells can be highly variable, and the impurities for biologics require several purification steps not needed for small molecules. In addition, different types of biologics use different unit operations to accomplish the manufacturing steps.

Successful Transition from Bench to Clinical-Scale Manufacturing (Milligram to Gram Scale) Requires:

- **Suitable cell line**
- **Developing and communicating upstream and downstream processes and conditions**
- **In-process testing and analytical methods defining identity, purity, potency, and quality**
- **Formulation**
- **Lot release and stability test methods (especially potency assays)**
- **Characterization methods**

Figure 1 illustrates the iterative nature of the development of the manufacturing process for a biologic, which includes genetically engineering a cell to produce the biologic, multiple steps for purification of the biologic through chromatography resins, and associated testing throughout to ensure product quality, purity, and stability.

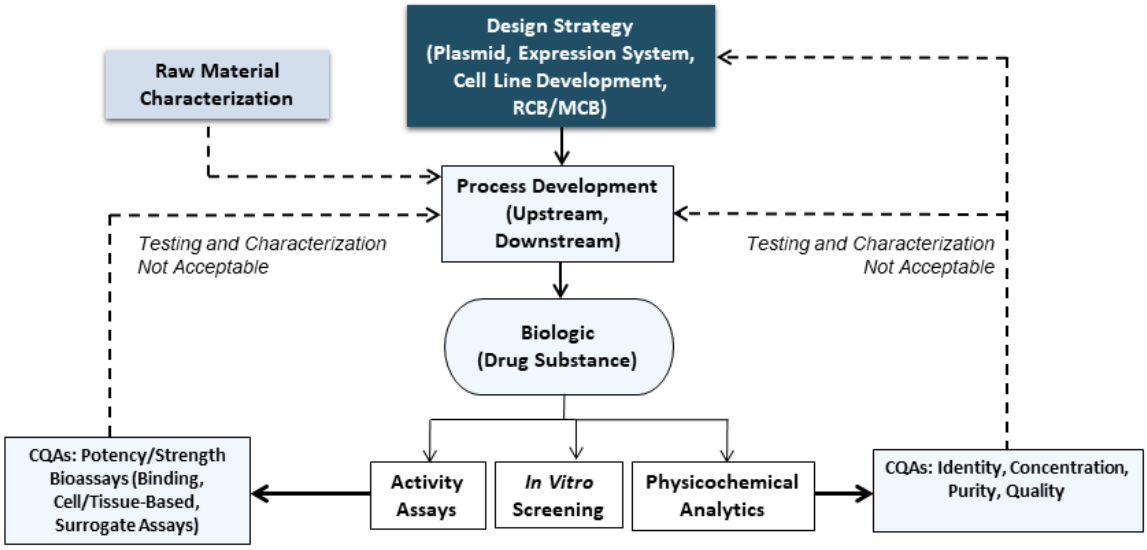


Figure 1. Iterative development activities for biological products

Biologics manufacturing, product characterization, and comparability protocols are more complex than those required for small molecule drugs. The manufacturing process for a biologic involves production in cells rather than chemical synthesis, and purification requires removing a wider range of product- and process-derived impurities. Characterizing a biological product needs an analytical "toolbox" that allows understanding the process and product. (Note that for vaccines, antigen characterization seeks to evaluate similarity to the wild

type—how "native" is the product?) In addition, the analytical tools must allow you to evaluate if a change in an attribute is significant. Finally, comparability studies use these analytical tools to demonstrate control and consistency of the manufacturing process, which provides information to support scale-up, and process and facility changes.

Resource:
NIH SEED: Navigating FDA: Drug Development Requirements

2.1 Scalability of Lab-Developed Process

The goal of optimizing the upstream (cell culture or fermentation) and downstream (purification) processes and **unit operations** for biologic DS production is to:

- Yield sufficient purified material
- Establish consistent, controlled, and scalable processes
- Determine product-specific attributes, in-process impurities, and analytical methods
- Develop process knowledge that informs larger scale manufacturing campaigns

A robust and consistent upstream process that minimizes variability is key to a robust and consistent downstream process and biologic product. Because this process is aimed toward manufacturing, the properties or attributes of the desired products dictate the selection of a production system. Process design and development is impacted by business needs and regulatory constraints. In addition, appropriate risk assessments need to be conducted and well documented throughout process development.

2.2 Development of an Expression/Transfection Vector

The process of developing stable cell lines often starts with expression vectors transfecting selected host cells (e.g., **CHO or HEK 293** cells, yeast, or *E. coli*), with desired plasmid DNA or viral vectors. The design and development of expression vectors encoding the appropriate sequence of genetic elements (gene of interest/insert gene, expression cassettes, selection markers, inserts and enhancers/promoters, tags) is key for early development and project initiation.

The amplification and expression of these engineered vectors in an appropriate host cellular expression system/cell line will ultimately determine the molecular attributes of the final product and its suitability to optimally assemble, post-translationally modify, and express recombinantly the encoded biologic product.

2.3 Expression System for Cell Line Developments

To accelerate filing an IND application for proof-of-concept clinical studies, it is becoming increasingly necessary for a company to deliver its pipelines efficiently by utilizing streamlined cell culture platform processes that include standardized process conditions and procedures. Titer is the primary benchmark characterizing upstream manufacturing efficiency, with higher titers generally indicating that more desired product is manufactured using the same or less amount of fluid or filled bioreactor volume.
The choice and use of a platform process can expedite early-stage cell culture process development activities, e.g., clone selection, process lock, and **technology transfer** to clinical manufacturing.

Key attributes of an appropriate expression platform and cell line for biologic product development are:

- Scalability and stability
- Ability to control clone selection and process changes
- Production of high-expressing and stable cell clones
- Engineered expression vectors should enhance stable target gene expression levels

Since changes in production cell lines during clinical development are considered major process changes, product comparability must be demonstrated if the cell line is changed during late-stage development. Changing the cell line after the Phase III clinical study typically requires additional human clinical studies. It is important to select the optimal clone prior to Phase III production of DS, and preferably at the Phase I stage.

Resources:
FDA: Q5D Quality of Biotechnological/Biological Products: Derivation and Characterization of Cell Substrates Used for Production of Biotechnological/Biological Products
Article: Optimizing Cell Line Development for High-Quality Biologics

2.4 Development of a Suitable Producer Seed Cell Line/Cell Bank

The process of banking cells generally moves from development of a research cell line and **research cell bank** (RCB) based on a clone of interest to establishment of a **master cell bank** (MCB), from which working cell banks can be produced. Especially for biotechnology startups, preparation of an MCB can involve a significant jump from work performed in standard laboratory conditions to good manufacturing practice (GMP)-compliant operations. MCBs also must undergo rigorous characterization testing to ensure the purity, safety, functionality, and genetic stability of cells grown from those banks. Consequently, biopharmaceutical developers usually delegate MCB preparation to contract development and manufacturing organizations.

MCBs must undergo rigorous characterization testing and qualification to ensure the purity, safety, and clearance of adventitious agents. This demonstrates functionality and genetic stability.

Resources:
NIH SEED: Basics of Interactions with FDA
FDA: INTERACT Meetings
FDA: Guidance on Drug Master Files
FDA: Characterization and Qualification of Cell Substrates and Other Biological Materials Used in the Production of Viral Vaccines for Infectious Disease Indications
FDA: Q5D Quality of Biotechnological/Biological Products: Derivation and Characterization of Cell Substrates Used for Production of Biotechnological/Biological Products
FDA: Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products
U.S. Pharmacopeia: USP<1032> Design and Development of Biological Assays
Article: Best Practices for Selecting a Top-Quality Cell Line

2.5 Bioprocess Development

An optimized, well-designed upstream and downstream lab-scale process is the basis for smooth tech transfer to a **current Good Manufacturing Practice** (cGMP) facility. Optimization mostly involves titer and yield improvements, which generally correlate with bioprocessing cost savings—this is something most commercial-scale manufacturers work to improve. Although upstream titers have improved significantly in recent years, the same can't be said for downstream yields.

Upstream Process (USP) Development: USP optimization should be conducted systematically and using a risk-based approach to develop a consistent process and product. Factors such as cell culture media and raw materials, cell culture conditions and operating ranges will have to be determined and modulated to identify and define the USP parameters for optimal cell growth, cell density, viability, and productivity/harvest titer (yield). These parameters facilitate the ability to scale up and produce the desired biologic product with TPP-aligned molecular attributes.

The focus is titer optimization, which is the amount (mass, measured as weight) of an expressed agent—generally a protein in aqueous solution—relative to the volume of total upstream-produced liquid containing the agent (with the bioreactor volume often used for this amount). Titer data are provided in terms of grams per liter (g/L).

An optimized, well-designed upstream and downstream lab-scale process is the basis for smooth tech transfer to a cGMP facility.

Downstream Process (DSP) Development: Development of a robust and consistent DSP must include the ability to understand and balance the output from the interconnected upstream process. During upstream production, there is a tendency to overly focus on product titers, but other factors such as cell concentration, cell viability, and various product quality characteristics may be impacted to achieve those high titers. And these upstream factors will most likely impact the subsequent recovery and purification process steps. To achieve a high-quality biologic product that is safe, it is important that the DSP unit operations can efficiently remove all in-process impurities (including host cell proteins [HCPs], nucleic acid, adventitious agents). The sequence and operating parameters of DSP chromatographic capture/purification and polishing steps—including viral inactivation and viral clearance—will be determined, fine-tuned, and optimized based on the biologic properties and characteristics.

The focus is yield optimization. Yield refers to downstream efficiency and is the ratio of mass (weight) of final purified protein relative to its mass at the start of purification (output/content from upstream bioprocessing).

To achieve a high-quality biologic product that is safe, it is important that the DSP unit operations can efficiently remove all in-process impurities (HCPs, nucleic acid, adventitious agents).

The objective of USP and DSP development is to build robustness and demonstrate control of a manufacturing process to ensure consistent biological products within the specifications of the manufacturing quality

attributes. The new regulatory expectation and **quality by design** (QbD) principles also reinforce the need for a systematic process development approach and risk assessment to be done early and throughout the development. Biologics DP manufacturing processes and unit operations need to be well understood and characterized in terms of different stresses and **critical process parameters** (CPPs) that would impact the **critical quality attributes** (CQAs).

The biopharmaceutical development and manufacturing strategies for biologic products are guided by the product's TPP. QbD principles are applied from the onset of product definition and development and are intended to ensure that:

- The product is designed to meet patient needs and efficacy requirements
- Critical sources of variability are identified and controlled through appropriate control strategies
- The process is designed to meet product CQAs consistently
- The process is continually monitored, evaluated, and updated to maintain product quality throughout its life cycle

Potential CQAs are selected based on prior knowledge and current understanding of structure-function relationships for the biological product candidate. A risk-assessment tool is developed and applied to each quality attribute. CMC-related activities focus on refining structure-function relationships and their impact on safety and efficacy. As new information becomes available throughout the product life cycle, it is used to iteratively update the quality attribute risk assessments, CQA classifications, and acceptance criteria.

Two industry- and regulatory-led case studies that apply QbD principles to developing and manufacturing an example A-Mab and A-VAX, are available. These case studies are highly detailed and provide a roadmap for biologics development.

Resources:

FDA: Q7A GMP Guidance for API
FDA: Q5A Viral Safety Evaluation of Biotechnology Products Derived From Cell Lines of Human or Animal Origin
FDA: Q5D Quality of Biotechnological/Biological Products: Derivation and Characterization of Cell Substrates Used for Production of Biotechnological/Biological Products
FDA: Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products
FDA: Q11 (Development and Manufacture of Drug Substances)
ICH: Q5C Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products
Article: Manufacturability Assessment–A Tool for Effective and Transparent Decision-Making and Efficient Process Development

2.6 Analytical Methods/Testing

For licensing of biopharmaceuticals, development, and validation of assays for lot release and stability testing must be included in the specifications for the DS and/or DP. Most importantly, a potency assay is required. Potency is the quantitative measure of biological activity, and ideally it measures the ability of the product to

elicit a specific response in a disease-relevant system. The activity measured in the assay must represent the intended biological effect (a.k.a. mechanism of action) and be related to the clinical response (if possible). The assay "toolbox" should be capable of discriminating product batches based on the following criteria:

- Amount of the active ingredient is sufficient to induce the biological effect
- Sub-potent batches can be identified (including storage under accelerated conditions as well as forced degradation studies)
- Consistency of the DS and DP is ensured (e.g., batch-to-batch and during the proposed shelf-life)

Robust and optimized analytical assays and characterization methods with well-documented procedures facilitate smooth technology transfer for process development and cGMP manufacturing.

A comprehensive analytical characterization package is also critical for managing process (or facility) changes in the development cycle for a biologic. As part of creating the manufacturing process, you should conduct analytical tests capable of qualitatively and quantitatively characterizing the physicochemical, biophysical, and bioactive/functional potency attributes of the active biological DS and formulated DP. Doing so will help ensure that the regulators have confidence in the equivalence and stability of the new DP throughout development and post-approval: in other words, comparability of the new DP with the previous DP. Such "comparability studies" are key to ensuring that a manufacturing process change will not have an adverse impact on the quality, safety (e.g., immunogenicity), or efficacy of a biologic or biopharmaceutical product.

Robust and optimized analytical assays and characterization methods with well-documented procedures facilitate smooth technology transfer for process development and cGMP manufacturing.

The analytical tests selected should provide information about the identity (primary and higher order structures), concentration, purity, and in-process impurities (residual host cell protein, mycoplasma, bacterial and adventitious agents, nucleic acids, and other pathogenic viruses). They should also provide information about process intermediates or altered product (clipping, proteolytic cleavage, degradation products), quality (endotoxins, sterility, particulates), solubility, and potency of the DP. Values for these characteristics will be determined during the scale-up of manufacture and are applied throughout the lifecycle of the DP. Importantly, they will support the manufactured products, CQA, **Certificate of Analysis** (CoA), and product lot/batch release. As shown in Figure 2, the analytical tests support all stages of process development, including formulation.

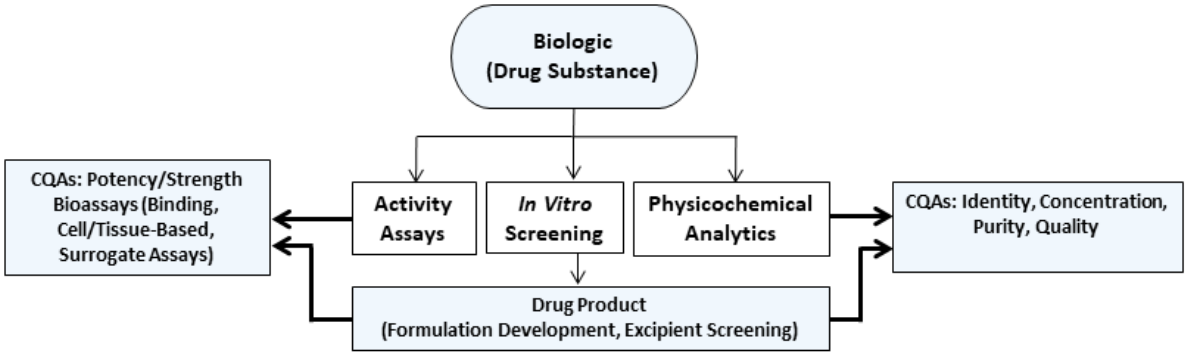


Figure 2. Integration of analytical and formulation evaluation in parallel in biologics development

Analytical data alone can confirm the comparability of the current product to a previous version of the product. Analytical comparability protocols are used for "specified" or "well-characterized" biologic products such as mAbs. These protocols facilitate approval of process or facility changes without a clinical trial and are prospective for documenting process changes. The challenge for biologics is that you cannot always predict if a change matters. The goal of the protocol is focused testing rather than "testing to infinity," and moreover a testing strategy validated with known samples with a known difference in performance.

How do you claim comparability? There are two parts to comparability—demonstrating process comparability and product comparability. For product comparability, the objective is to monitor clinically relevant structural features that are desirable product properties. The emphasis is on release assays and structure (conformation) during manufacture and storage. You establish limits prospectively to define potential deviations from comparability (which provides rigor and credibility). There are two types of limits, and the limits must be sufficiently rigorous but not so tight as to cause "nuisance alarms:"

- Acceptance Limits–excursion generally means failure to demonstrate comparability
- Alert Limits–excursion results in an investigation but is not deemed a failure *a priori*

Acceptance and alert limits usually apply to release tests and process validation CQAs (especially impurities). For product characterization methods, alert limits typically apply. In addition, qualitative comparisons are used for some characterization tests (especially melting and spectral curves).

In the ideal case for a comparability strategy, you have two samples that differ in characterization data, process source, potency, and (rarely) clinical performance. This information will validate that the assays are sensitive to significant process changes. Establishing a statistically meaningful correlation of the potency assay with efficacy and stability is essential. For vaccines, defining antigenicity and immunogenicity by neutralization and linear epitopes determines if process changes impact product quality.

You need to plan to assess comparability and manage deviations appropriately. This plan could include a comparison of staff, chromatography resins, and purification processes in different facilities that are performed using the same raw materials.

Resources:
FDA: Q5E Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process
FDA: Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products
FDA: Q7A GMP Guidance for API
FDA: Analytical Procedures and Methods Validation for Drugs and Biologics

2.7 Optimizing Delivery by Desired Route of Administration

Formulation of a DS typically involves combining an active ingredient and one or more excipients; the resultant **dosage form** determines the route of administration, drug delivery strategy, and clinical efficacy and safety of the drug.

In the case of biologics, formulation is challenging and requires a clear understanding of the physicochemical properties and molecular complexity of the biologic. Given the diversity and differentiation of product types, careful consideration should be given to the product presentation, intended dosage form configuration, route of administration, designated delivery device component, and sensitivity to external stress, shear forces, and storage conditions.

The formulation studies should evaluate the impact of other ingredients beyond the biologic active ingredient/DS on the biological product candidate's ability to get where it is needed. Formulation can influence manufacturability, optimal therapeutic delivery and efficacy, pharmacokinetics, safety, and product presentation (parenteral or inhaled/nasal delivery). Formulation strategies must be devised (and aligned with the TPP) based on the product type to ensure the product potency, stability and shelf life, pH, tonicity, and other molecular and structural attributes when mixed with **excipients** and adjuvants.

Optimal formulation development can be built on QbD principles, and initial risk assessment of the critical or interacting formulation variables—such as product concentration, buffers, pH and tonicity, surfactant, preservatives, product uniformity, and degradation products—should be extensively monitored by analytical assays. The ICH Q6 Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products and Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/ Biological Products guidelines discuss the types of tests and acceptance criteria that are appropriate for certain dosage forms/formulations.

Resources:
FDA: Co-Development of Two or More New Investigational Drugs for Use in Combination
FDA: Drug Products Including Biological Products that Contain Nanomaterials
FDA: Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients
Article: Biologic Excipients: Importance of Clinical Awareness of Inactive Ingredients
Article: Excipient Selection Biologics Vaccines Formulation Development

2.8 Lab-Scale Production for *In Vitro* and Small Animal *In Vivo* Studies

Lab-scale production for *in vitro* and small animal *in vivo* studies are the same for small molecules and biologics.

For a discussion of the requirements and processes, please refer to Section 3 of the Regulatory Knowledge Guide for Small Molecules.

Resource:
FDA: An FDA/CDER Perspective on Nonclinical Testing Strategies: Classical Toxicology Approaches and New Approach Methodologies (NAMs)

2.9 Technology Transfer Readiness

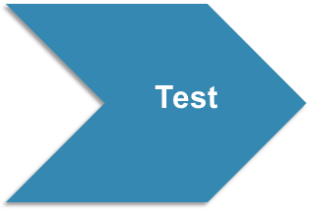
Biologics have more complicated structures and manufacturing processes than small molecules and are generally a more challenging technology to transfer.

Technology transfer is a systematic procedure to pass the documented knowledge and experience gained during development (or commercialization) to an authorized party. Through this transfer, a donor (the team sending the information) site transmits proprietary knowledge and expertise about a product, its manufacturing process, and the analytical methods to a receiving (the team accepting the information) manufacturing site. Technology transfer is critical in any drug development program, occurring for various reasons and at different development stages. For example, an innovator may be looking for clinical trial manufacturing, for commercial-scale manufacturing, or to replace a site with quality issues.

How you handle a technology transfer can significantly impact the success of a product's development and, ultimately, commercial manufacturing. The donor and receiving sites must gather and prepare several documents in sufficient detail to ensure a successful technology transfer of a biologic. These can include:

- Technology transfer plan
- Detailed analytical and formulation methods
- Manufacturing process description or batch record
- CPPs
- CQAs
- Technical gap analysis
- Adequate change control management system

A successful transfer allows the receiving site to carry out the activities to produce the product on the proper scale for the stage of development. In addition, this knowledge forms the basis for the manufacturing process, control strategy, process validation approach, and ongoing continual improvement.



3 Studies in Small Animals for Biologics

Developing biologics and investigating their **absorption, distribution, metabolism, excretion, and toxicity** (ADMET) properties is very different from traditional, low molecular weight drugs. Refer to Sections 1 and 2 of the Regulatory Knowledge Guide for Small Molecules for a discussion of the key concepts that also apply to biologics.

Biologics present unique issues, necessitating a flexible, case-by-case, science-based approach to preclinical testing. The FDA adopted the ICH S6 Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals and S6 Addendum to Preclinical Safety Evaluations Guidance for Biotechnology-Derived Pharmaceutical, which describes the unique approach needed to select animal species and immunogenicity testing and outlines typical preclinical testing. Early characterization should include **maximum tolerated dose**, **no-observed-adverse-effect-level** (NOAEL)**,** pharmacology, and *in vivo* efficacy. Because biologics are highly target-specific, their side effects are mostly related to exaggerated pharmacological effects. This contrasts with small molecule drugs which are more disposed to induce harmful off-target effects.

All vertebrate animal research must be conducted following the Public Health Service Policy on Humane Care and Use of Laboratory Animals and has the **Institutional Animal Care and Use Committee** (IACUC) approval status.

Animal research involves the collection of data from carefully designed experiments. The validity of the research and the conclusions drawn from the data are influenced by many factors. Some of these factors may confound experimental results and therefore must be carefully considered in the testing strategy and, where possible, controlled.

Key Factors to Consider When Developing an Animal Testing Strategy

- **Target patient population and duration of dosing**
- **Formulation of the product and route(s) of administration intended for humans**
- **Known pharmacology and toxicity of the product and similarity to other products in structure or activity**
- **Selection of specific studies, test species/test system and dose levels**
- **Data from *in vitro* assays including off target effects that that can help identify the risks**

Biologic-Specific Considerations

Regarding routine preclinical testing for biologics, innovators usually perform pharmacodynamic (PD) studies that measure the product candidate's pharmacologic activity and define its mechanism of action. Biologics typically also undergo single- and repeat-dose toxicity studies using relevant species. Safety pharmacology studies (to evaluate the product candidate's functional effects on specific organs and major body systems) and local tolerance testing can be done separately or in **toxicity testing**. Innovators ordinarily perform single- and multiple-dose pharmacokinetic (PK) and/or **toxicokinetic studies** to explore dose-response relationships and evaluate absorption, clearance (especially antibody-mediated clearance), disposition, and exposure. These studies help establish a safety margin in humans. Immunogenicity testing using screening and mechanistic studies should be considered even though animal models are not predictive of human immunogenicity.

Standard carcinogenicity bioassays are generally inappropriate for biologics. However, the S6 guidance calls for carcinogenicity assessment when warranted based on the "duration of clinical dosing, patient population, and/or biological activity." You can consider several approaches to assess risk, including testing in various malignant and normal human cells and additional testing in relevant species if concern exists regarding the

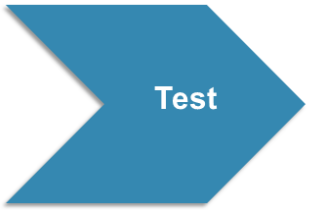
carcinogenic potential.

Depending on the product candidate, clinical indication, and intended patient population, reproductive and developmental toxicity studies may or may not be recommended following ICH S6—such studies using primate species are challenging because of these animals' heterogeneous drug responses.

Classic biotransformation studies are unnecessary because biologics generally degrade into peptides and amino acids.

Genotoxicity studies also usually do not apply to biotechnology-derived drugs because they are not expected to interact with DNA or chromosomes.

Resources:
FDA: The Beginnings: Laboratory and Animal Studies
Tool: Mouse Genome Informatics
FDA: Addendum-Preclinical Safety Evaluation of Biotechnology Derived Pharmaceuticals
FDA: Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals
FDA: S7A Safety Pharmacology Studies for Human Pharmaceuticals



4 IND-Enabling Studies

IND-enabling studies are conducted to evaluate potential toxicity risks prior to human studies and to estimate starting doses for clinical trials. Requisite IND-enabling studies for an IND application include pharmacology, pharmacokinetics, and toxicology assessments. IND-enabling non-clinical studies are typically conducted in both small animals (rodents) and large animals (non-rodents) which may or may not be genetically modified. The goal of these studies is to validate the drug-target interaction, and predict the drug pharmacology, **pharmacokinetics**, **pharmacodynamics**, therapeutic efficacy, and potential toxicity safety concerns for the new molecular entity. Larger-animal IND-enabling studies conducted in a contract facility under cGMP with full documentation, require an optimized drug formulation administered in the same manner as the anticipated first-in-human trial. Refer to Section 2 in the Regulatory Knowledge Guide for Small Molecules for additional information.

IND-Enabling Studies

- **Define the starting dose regimen**
- **Define the maximum tolerated dose**
- **Align and identify the optimal and clinical route of administration**
- **Guide human dose selection for initial clinical trials**
- **Justify species selection for safety assessment**

Depending on the product type, review general guidelines for non-clinical assessment of biological products as appropriate to help in the non-clinical evaluation of specific products.

Biologic-Specific Considerations

Most biologics cannot be tested in commonly used animal species, such as rats and dogs, because of their biological activity and species- or tissue-specific activity. To identify a "relevant species," you must use a variety of tests, such as *in vitro* binding assays and functional tests. A "relevant species" is one where the expression of a receptor or an epitope (in the case of mAbs) allows the test material to be pharmacologically active. Usually, you identify two relevant species, although one species may suffice when the product's biological activity is well understood, or only one appropriate species exists.

In some cases, identifying an appropriate species might be impossible. For example, the chimpanzee (which cannot be sacrificed at the end of the study) is the only relevant species for some test materials. Consequently, you may need to consider alternative approaches to gathering animal data, including transgenic animals that express the human receptor or homologous proteins (which recognize the target protein or epitope in the animal).

Several biologics elicit immune responses that can affect preclinical study results. In some situations, these effects are desired (e.g., with a vaccine), but unwanted immunogenicity could be harmful. Potential undesired effects include cross-reacting with endogenous substances, neutralizing or prolonging the biologic's activity, or forming immune complexes. Usually, you obtain necessary samples for antibody testing during repeat-dose toxicity studies. Therefore, when interpreting the data, consider the effects of antibody formation on PK, PD, and adverse events.

Detection of ADA does not usually end a preclinical study unless the immune response neutralizes the biologic product candidate's effects in a significant fraction of the test animals. However, be aware that an animal's immune responses are not predictive of those in humans.

Resources:
FDA: Regulatory Considerations in the Safety Assessment of Adjuvants and Adjuvanted Preventive Vaccines
EMA: S6R1 Preclinical Safety Evaluation for Biotechnology Derived Pharmaceuticals
FDA: ICH guidance on M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals
WHO: Guidelines on Nonclinical Evaluation of Vaccine Adjuvants and Adjuvanted Vaccines

DNA Vaccines Resources:
FDA: Plasmid DNA Vaccines for Infectious Disease Indications

Monoclonal Antibodies Resources:
FDA: Nonclinical Safety Evaluation of the Immunotoxic Potential of Drugs and Biologics
FDA: Nonclinical Safety Evaluations of Drug or Biologic Combinations

4.1 Optimal and Consistent Production of Biologic Product Formulation

It is important that the new biologic product is made using a process that produces a consistent formulation and demonstrates consistent results in testing. At the discovery stage, non-clinical data drive lead molecule and formulation optimization.

If significant changes are introduced during scale-up, bridging studies re-validating basic attributes may be needed to identify any changes in key characteristics.

Resources:
FDA: ICH Q8(R2) Pharmaceutical Development
FDA: Q11-Development and Manufacture of Drug Substances
FDA: Q5D Quality of Biotechnological/Biological Products: Derivation and Characterization of Cell Substrates Used for Production of Biotechnological/Biological Products
FDA: Guidance for Quality by Design
EMA: ICH Q6B: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products

4.2 Suitability and Dosing Regimen Studies in Non-Clinical Large Animals

Refer to Section 2.2 in the Regulatory Knowledge Guide for Small Molecules for information on selection of appropriate large animal models.

It is important for the animal model selected to inform the safety data for FDA. This means the animal model should replicate the human model as much as practical. Wild type animal models may not be appropriate and, in those cases, genetically modified animals or humanized transgenic animals may be used to validate biologic drug-target interaction and drug activity in the target disease.

Per FDA Guidelines, justification for species selection or appropriateness of the species for pharmacology, safety, and toxicokinetics testing should consider:

- **Pharmacology: Is the pathway and/or target active and relevant in the species relative to humans?**
- **Expression: Is the expression of the target receptor similar across tissues in this species? If not, will this interfere with interpretation of the study and extrapolation to humans? Is the homology between interspecies and comparability of molecular attributes in different species?**
- **Potency: Is the potency of the agent at the receptor similar across species? Potency assays should be conducted in pharmacology model(s), toxicology species, and humans. One can look at sequence alignments to get an idea of the similarity of the target across species as well.**
- **Metabolism: Human metabolites need to be covered in the toxicology species.**
- **Toxicology: Is the species selected sensitive to a particular biologic class and the toxicological mechanism relevant for humans?**

Biologics may exhibit a varying degree of species specificity. Healthy animal models may not be able to successfully validate the drug targets or model a disease or disease mechanism, providing only limited functional information about the effect of the drug on disease indication.

Resources:
FDA: M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals

4.3 GLP Toxicology Studies

As with small molecule drugs, you must conduct **good laboratory practice** (GLP) toxicology studies prior to the submission of the IND application. For a more complete discussion about the requirements and processes, please refer to Section 2.3 of the Regulatory Knowledge Guide for Small Molecules.

Of special note with biologics, the design of the GLP **toxicology study** and the selection of the experimental protocol should be defined on a case-by-case basis. They should be tailored to the indication and responsiveness to the route of administration and provide enough information to evaluate the risks and safety of the candidate substance.

Resource:
EMA: ICH-S6R1 Preclinical Safety Evaluation Biotechnology Derived Pharmaceuticals

4.4 FDA Input on the Toxicology Study Plan

For best practices and guidance on your biologic toxicology study plan, please refer to Section 2.3 of the Regulatory Knowledge Guide for Small Molecules.

Initiating early FDA conversations and having a clear understanding of the regulatory requirements for the proposed DP facilitates an effective development pathway.

Resource:
FDA: CDER Pre-IND Consultation Contacts
NIH SEED: Basics of Interactions with FDA (CDER/CBER)

4.5 Contract Research Organization (CRO) Selection for GLP Studies

Innovators of biologics should follow the guidance for selecting a **CRO** facility as outlined in Section 2.4 of the Regulatory Knowledge Guide for Small Molecules.

5 Pilot Scale Manufacturing

Pilot-scale manufacturing produces a batch of DP during development at a volume sufficient for pre-clinical studies, stability testing, and related quality testing

required by the development program. The pilot-scale batch includes excipients reasonably anticipated to be clinically safe and is made available in containers suitable for development studies. The pilot-scale batch does not need to comply with cGMP. Most of the considerations for pilot-scale manufacturing are similar for small molecule drugs and biologics. For a more complete discussion of pilot-scale manufacturing, please refer to Section 3 of the Regulatory Knowledge Guide for Small Molecules.

Biologic-Specific Considerations

Manufacturing a **pilot batch** for biologic DS and formulated biologic DP demonstrates scalability from lab scale to a fraction (typically 10%) of commercial scale, and reproducibility of cell culturing as well as the upstream process and downstream unit operations**.**

Product development and phase-appropriate manufacturing processes should achieve a suitable product quality and safety profile for Phase I investigational drugs and beyond.

Carefully designed bioprocesses tend to scale linearly in the five-to-ten-fold range in moving in steps from lab scale to pilot scale and commercial scale. CPPs and CQAs tend to change at larger scales so be careful to monitor process and product comparability and adjust the process accordingly. Biologics can be particularly problematic, as there are so many variables involved with living organisms. There also are different problems that arise whether a company is working with mammalian or microbial cells. Product development and phase-appropriate manufacturing processes should achieve a suitable product quality and safety profile for Phase I investigational drugs and beyond.

Depending on the size of the pilot batch, the material can be used to support different continued development efforts such as developing or optimizing analytical methods, preliminary stability studies, non-clinical animal studies, bridging studies, or, if sufficient material exists, it may replace the original **reference standard**.

5.1 Chemistry Manufacturing Controls (CMC) Plan Outline

There are no specific templates or guidance documents describing best practices for CMC planning for new biologics. Refer to Section 3.1 of the Regulatory Knowledge Guide for Small Molecules for a discussion of the key concepts that also apply to biologics.

The unique developmental characteristics, formulations, indication, patient population, and other factors all contribute to the scale and requirements for each new biologic drug. It is imperative that quality and regulatory groups are actively involved in all CMC strategies and decision points leading to actions. FDA will review the CMC in the IND and will evaluate it based on the safety of a product and the suitability of the manufacturing process to produce consistent DS and DP. Developers are encouraged to seek CMC and regulatory expertise (and FDA guidance) early to provide valuable guidance in preparation of an optimal CMC strategy.

In addition, elements of the manufacturing process and process controls will be extended to interconnected and supporting processes starting from expression vector production, cell line development and vials of the RCB and MCB, suitability and stability of engineered cell banks, cell culturing and **harvest material**, and purification and modification reactions. Some common components of a CMC plan also include CQAs, scalability and cGMP

manufacturing, fill/finish, formulation and analytical development, product release specifications, regulatory compliant stability studies for DS and DP, control strategy and CPPs, clinical trial material projections, storage and distribution, project management, raw material sourcing, QMS development, and regulatory documentation required for IND filing (batch records, analytical test methods, process flow diagrams/maps, etc.). In all cases, it is important for you to educate yourself, or to use external expertise, about conducting development work in a way that will be acceptable to regulators.

Traditionally, biomanufacturing development is split into upstream and downstream functional groups/operations. Early collaboration and open communication between upstream and downstream functions are crucial to ensure a consistent end-to-end bioprocess. Additionally, linking upstream and downstream experimental studies benefits the analytical, product characterization, and formulation teams by providing them with material for their studies earlier.

Resources:
FDA: M4 Organization of the Common Technical Document for the Registration of Pharmaceuticals for Human Use

5.2 Biologic Candidate Characterization

Product characterization is the foundation for successful biological drug development. Early understanding of the biological product, particularly its structure-function relationships and heterogeneity, can ensure the right choices are made at key milestones during product development. Development activities should focus on establishing physicochemical and biological characteristics of the active biologic DS and the formulated DP. In-depth knowledge of a product chemistry, structure, and biological activities facilitates easier process design to ensure the biologic drug attains critical product safety, purity, and potency, as per ICH Q6B.

Analytical test methods should be comprehensive, robust, accurate, and quantifiable and should help understand the links between structural properties and required CQAs of the DS and DP. The CQAs should demonstrate product identity, potency, purity, and safety. For example, during this stage, the biologic molecule's phenotypic, genotypic, and biochemical profiles must be confirmed/determined.

Analytical characterization should also determine:

- Structure identity and shape
- Amino acid/genetic sequence
- Morphology (electron microscopy)
- Size and molecular mass (SDS-PAGE, LC-MS, size exclusion chromatography)
- Isoelectric point (PI) and charge
- Disulfide and glycan analysis
- Other post-translational modifications

The biologic candidate's potency or functional bioactivity (ELISA or SPR/Octet bioassays) and mechanism of action, and any possible toxicity issues are critical characterization attributes that will need to be studied.

Significantly, for biologics, the process is the product, therefore characteristics and quality attributes are dependent on the precursor cell lines (cell banks) and process dependent (impurities). In-process and

bioanalytical testing and methods for cell culture, fermentation, and assays to determine harvest titers, process yields, or product stability become critical to support preclinical and clinical phase development. Additionally, the RCBs and MCBs must be fully tested and characterized for biosafety before they can be used for biologic process development.

It is critical to provide evidence of product equivalence based on molecular characterization (physicochemical and biophysical attributes) of the DS and DP among different batches when compared to a reference standard. This approach will be used for key activities such as stability, toxicology, and **clinical trials**. Ultimately, a subset of these analytical methods is used for lot release and stability testing with defined acceptance criteria for cGMP manufacturing of a DS and DP for clinical trials and to support comparability studies following changes in manufacturing.

Important CMC considerations in early development should include a comparison of phase-appropriate analytical methods against fully qualified methods, alongside a comprehensive understanding of the product's development history.

The IND must contain sufficient CMC information to permit the evaluation of safety. This information is vital for many biologics, which may raise concerns because of their product- and process-related impurity profiles or the use of materials with unknown components in their manufacture. The FDA recognizes that manufacturing processes can change as development progresses, and this can cause changes in product development.

Resources:
FDA: Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products
FDA: Q7A GMP Guidance for API
FDA: Q8(R2) Pharmaceutical Development
FDA: Q8, Q9, & Q10 Points to Consider, Questions and Answers from Training Sessions
EMA: Q6 Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products

5.3 Biologic Product Quantity Needed to Support Early Development Work

The amount of biological product required for early-stage activities tends to be greater by a factor of ten or more than needed for a small molecule in early development work. Refer to Section 3.3 of the Regulatory Knowledge Guide for Small Molecules for a discussion of the critical concepts that also apply to biologics.

The amount of biological product required depends on the type of biologic being developed—for example, in early development, proteins like mAbs need a lot more material (a total of hundreds of grams) than vaccines (a total of tens of grams) based on their mechanism of action. Amounts increase as a biologic candidate proceeds through translation into preclinical studies and early-stage bioprocess development. Formulation and analytical teams especially need ample material for biological development—formulation requires about a factor of ten more biological product for solubility and stability studies than analytical needs for product characterization and method development.

It's important to budget and plan to avoid limiting product supplies, which can slow progress toward the IND.

5.4 Contract Manufacturing Organization (CMO) Selection

Most of the considerations for selecting a CMO are the same for small molecule drugs and biologics. For a more complete discussion of CMO selection, please refer to Section 3.4 in the Regulatory Knowledge Guide for Small Molecules.

In the case of biologics products, contract manufacturing can cover the outsourcing of all—or only a part—of the manufacturing process for a product. You can choose to engage multiple CMOs; for example, (i) cell line development manufacturer, (ii) upstream/downstream process and BDS manufacturer, and (iii) final drug product packaging and performing release testing manufacturing.

Engaging (or not) a CMO is ultimately based on business requirements, funding available, internal manufacturing capabilities and capacities, and other strategic factors.

Resources:
FDA: Q9 Quality Risk Management
FDA: Q10 Pharmaceutical Quality System
Article: GMPs for Early Stage Development Projects

6 Clinical Scale Manufacturing

Most of the considerations for clinical scale manufacturing are similar for small molecule drugs and biologics. For a more complete discussion of clinical scale manufacturing, please refer to Section 4 of the Regulatory Knowledge Guide for Small Molecules.

Biological products are manufactured using relatively complex bioprocesses and different types of biologics use diverse unit operations in the bioprocess. The amount of biological product required to support a clinical trial will vary throughout development. Clinical batch production size will be determined by:

- Novelty of the biologic product
- Upstream expressed/harvest titers
- Downstream processed biologic product yield (product loss during purification)
- Final drug product concentration to achieve the therapeutic/clinical dose
- Material required for stability and other ancillary testing
- Nature and extent of clinical study (number of doses, number of participants, etc.)
- Comparative (bridging) studies as the bioprocess and scale change throughout development

Resources:
FDA: Q5E Comparability of Biotechnological/Biological Products Subject to Changes in Manufacturing
CFR: 21 Code of Federal Regulations 210.3
NIH: FDAAA 801 and the Final Rule

6.1 Manufacturing Biologic Product for Clinical Trials

Refer to Section 4.1 of the Regulatory Knowledge Guide for Small Molecules for an overview discussion

of the drug product manufacturing requirements for use in clinical trials.

First-in-human trials require less material than pivotal (efficacy) studies. All materials used in clinical trials must be manufactured in accordance with cGMP. However, FDA expects manufacturing processes to improve throughout clinical development, therefore cGMP expectations for a first-in-human trial are not identical to cGMP expectations for a pivotal study or marketing application.

Biologic-Specific Considerations

Biologics are far more sensitive to process changes than chemically synthesized drugs, and process changes have the potential to affect a biological product adversely. Expect some changes in the manufacturing process of biologics before approval (e.g., to scale up from lab scale to pilot production to full-scale manufacturing, improve manufacturing efficiency, or change the production facility) and plan for comparability studies to evaluate these process or facility changes. FDA will determine if additional studies are required to ensure the quality of the post-change biological product and suitability for the next stage of development—FDA has issued guidance that describes comparability studies.

6.2 CoA Parameters

Most of the considerations for selecting CoA items and setting specifications are similar for small molecule drugs and biologics. For a more complete discussion of CoAs, please refer to Section 4.2 of the Regulatory Knowledge Guide for Small Molecules.

For biologics, as appropriate to the product and process, CoAs for plasmid DNA, microbial culture, cell culture (master and working seed lots and/or RCB and MCB) should be provided in the IND. Minimum product description criteria in the CoA will vary depending on product type (vaccine, mAb, interleukin). See the box below.

Minimum CoA Descriptions

- Appearance
- Concentration/content/strength (UV absorbance and/or HPLC-based method)
- Identity (molecular weight/mass spec, vector genome identity, etc.)
- Quality (pH (if a solution), Osmolality (if a solution), visible particles (<USP 790>, Inspection of Injectable Products for Visible Particulates
- Quantity and quality, purity (HPLC-based methods (IEX, SEC, RP, capillary gel electrophoresis), SDS-PAGE, Western blots – Qualitative)
- Potency (ELISA or OCTET or SPR assay, cell-based assay, infectivity assay or viral genome/titer or in vitro expression)
- Compendial assays as appropriate
- Product specific impurities: variants related to monomers, dimers, aggregates, clipped species, degradation product etc.
- Process related impurities: residual host cell protein (HCP), mycoplasma, bacterial and adventitious agents, nucleic acids, other pathogenic viruses (based on cell lines used), residual Benzonase® endonuclease, etc.
- Endotoxin levels (set specifications): <USP85>
- Bioburden/Microbial limits: <USP 61>
- Excipient levels (if any)– HPLC-based impurity levels (organic or inorganic or leachable) as Detailed in Q3B Impurities in New Drug Products and Residual Solvents
- Sterility testing that may be needed dependent on dosage form (mostly liquid suspensions)
- Additional product characterization data (for information only) may also be included in the CoAs (information on glycan profile, disulfide bond, morphology (electron microscopy), charge/zeta potential, Circular dichroism, etc.)

Resource:
FDA: Biologics Post-Market Activities: Lot Release

6.3 Retaining Samples for Bridging Studies

A comparability/**bridging study** is performed to provide non-clinical or clinical data that allows extrapolation of the existing data from the DP produced by the current process to the DP from the changed process.

Retention samples serve as a record of the finished product or starting material batch and are retained for two purposes: a specimen for analytical testing and an example of the fully finished product. The considerations for samples retained to support bridging studies are the same for small molecule drugs and biologics. For a more complete discussion of retention samples, please refer to Section 4.3 of the Regulatory Knowledge Guide for Small Molecules.

Resource:
FDA: Information about Retention Samples

6.4 Real-Time and Accelerated Stability Data for Clinical Trials

Stability studies are mandated by regulatory agencies worldwide. They determine the shelf life and provide evidence that the quality of a drug product remains acceptable for the duration of its stipulated shelf-life and the length of a clinical trial.

Shelf life is commonly estimated using real-time and accelerated stability test results. In **real-time stability testing**, a product is stored at recommended storage conditions and monitored until it fails product specifications. In **accelerated stability testing**, a product is stored at elevated stress conditions (e.g., high temperatures, light, and humidity). Degradation at the recommended storage conditions can be predicted using known relationships between the acceleration factor and the degradation rate.
Refer to Section 4.4 of the Regulatory Knowledge Guide for Small Molecules for a discussion of the key concepts.

Biologic-Specific Considerations
Biologic drugs are highly complex molecules and are more susceptible to environmental factors than small molecules. In comparison with small molecules, biologics are more heat and light sensitive, tend to denature at surfaces, subject to enzymatic degradation, and aggregate under various conditions to form immunoreactive species (a potential safety issue). Therefore, stability testing studies are performed to evaluate biologics under a wider range of environmental conditions over a specific timeframe (e.g., to cover the length of a clinical trial). The results determine recommended storage and shipment conditions for DS and DP and the appropriate shelf life or retest period.

Establishing which analytical methods are stability-indicating is required in setting up a cGMP-compliant stability program. Also verify that analytical method qualification and/or validation is phase appropriate. In addition, evidence of the stability and recovery of the seeds and cell banks (RCB and MCB) should also be monitored and documented. This information—particularly the stability on process development batches and harvest—will be required in the IND submission package.

Resources:
ICH: Q5C Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products
FDA: Drug Stability Guidelines
FDA: Q1D Bracketing and Matrixing Designs for Stability Testing of New Drug Substances and Products

6.5 Manufacturing Biologics

Clinical trial material and commercial biological products are manufactured using cGMP, which is a system for ensuring that products are consistently produced and controlled according to quality standards within a QMS. cGMP and QMS are designed to minimize the risks involved in any pharmaceutical production that cannot be eliminated through testing the final product. Most of the considerations for cGMP manufacturing and a QMS are similar for small molecule drugs and biologics. For a more complete discussion of cGMP production, please refer to Section 4.1 of the Regulatory Knowledge Guide for Small Molecules.

cGMP ensures that biological products are consistently produced using optimized and controlled manufacturing processes. A cGMP facility should:

- Maintain a strong set of written (validated) process documents
- Hire and train staff appropriately for the tasks they will perform
- Document all activities as they occur
- Perform regular reviews of all activities
- Document discrepancies from standard processes
- Implement remediation plans for any issues consistently identified

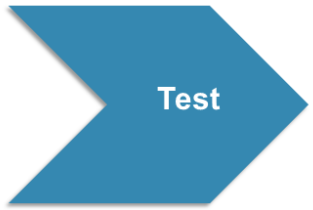
Biologic-Specific Considerations

cGMP production of biologics requires the implementation of robust and flexible integrated upstream and downstream processes that can be efficiently transferred and scaled up for production at all scales. Detailed analytics, characterization and in-process testing of such products is often defined by the manufacturing processes. Changes in the manufacturing processes, equipment, or facilities should be closely monitored as they could result in changes in the biological product itself. In some cases, additional clinical studies are required to demonstrate the product's safety, identity, purity, and potency.

The production of biologics is monitored by FDA from the early stages to ensure the final product turns out as expected. For this reason, the manufacture of biological products must adhere fully to cGMP for all production steps, beginning with those from which the active ingredients (working cell bank, expression vectors/plasmid DNA, culture media, etc.) are produced. Start-up companies are usually best served by engaging production facilities that satisfy the necessary requirements. Developers are encouraged to seek CMC and regulatory expertise (and FDA guidance) early in the process. They can provide valuable guidance during a cGMP manufacturing campaign.

If you choose to self-manufacture the DP, rather than contracting with an external party, the FDA documents included in the resources (below) outline many of the requirements for establishing a full quality system.

Resources:
FDA: Q7A GMP Guidance for API
FDA: Q8(R2) Pharmaceutical Development
FDA: Q9 Quality Risk Management
FDA: Q10 Pharmaceutical Quality System
FDA: cGMP: Phase I Investigational Drugs
FDA: Questions and Answers on Current Good Manufacturing Practices—Production and Process Controls
FDA: Q5E Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process
FDA: cGMP for Outsourcing Activities and Facilities
EMA: Guideline, Strategies to Mitigate Risks First in Human Early Clinical Trials
Article: GMPs for Early Stage Development Projects



7 Initiating First-in-Human Clinical Trials

Clinical trials are conducted to determine the risks and benefits of a new drug in humans. The requirements and guidelines for setting up and testing new small molecule drugs and biologic drugs in clinical trials are the same.

For a more complete discussion of initiating clinical trials, please refer to Section 5 of the Regulatory Knowledge Guide for Small Molecules.

8 Market Scale Manufacturing

Selecting the appropriate manufacturing scale to meet your process yield, titer, and product demand helps ensure that you can satisfy product demand at launch. The considerations for market-scale manufacturing are the same for small molecule drugs and biologics. For a complete discussion of market scale manufacturing, please refer to Section 6 of the Regulatory Knowledge Guide for Small Molecules.

By the time a drug is being distributed for clinical trials, the DS should be consistently produced using cGMP at gram/kilogram scale and formulated for optimal delivery as a final finished DP. At the commercial stage—and depending on the biological product type—multi-gram to kilogram batches is typical. Manufacturing may occur at multiple sites and in multiple countries or continents.

CMOs are often engaged to support scale-up activities. As discussed above (see Section 5.4 on CMO selection), you may engage different CMOs for pre-IND manufacturing, clinical production, and commercial scale production. In all cases, CMOs should be capable of meeting production needs in both scale and timing. CMOs should also provide appropriate documentation to support regulatory filings.

8.1 CMO Manufacturing Guidelines

As is the case with small molecule drugs, if you use a CMO you remain responsible for product quality, safety, efficacy, and cGMP compliance. For a more complete discussion of CMO guidelines, please refer to Section 6.1 and Appendix A of the Regulatory Knowledge Guide for Small Molecules.

8.2 Manufacturing Batch Record

The **manufacturing batch record** (MBR) documents all process and quality attributes: information about raw materials, in-process control tests/values, and release tests/values that describe the manufacture of a DS or DP. The considerations for MBRs are similar for small molecule drugs and biologics. For a more complete discussion of MBRs, please refer to Section 6.2 of the Regulatory Knowledge Guide for Small Molecules.

Biologic-Specific Considerations

If manufacturing changes are implemented in the product or production process, quality controls, equipment and facilities, or labeling, you must notify FDA about each change to an approved BLA (post approval changes) under 21 CFR 601.12.

A systems-based risk-management approach to identifying critical elements common to making biological DP is described in 7345.848 - Inspection of Biological Drug Products, Compliance Program Guidance (Chapter – 45 Biological Drug Products).

Resource:
CFR: 21CFR211 Current Good Manufacturing Practice for Finished Pharmaceuticals

8.3 Biologic Product CoA

Certificates of Analysis provide an overview of test results obtained from an intermediate, DS, DP, or raw material. The CoA also includes the assessment of compliance with the specifications for the attributes. The considerations for CoAs are similar for small molecule drugs and biologics. For a more complete discussion of CoAs, please refer to Section 6.3 of the Regulatory Knowledge Guide for Small Molecules. Also, see Section 6.2 of this guide for more information on biologic CoA parameters.

Biologic-Specific Considerations

For **Phase I** products/clinical trials, robust qualified assays should be developed and considered. Qualified end-product testing can be focused on a limited number of attributes after demonstration of adequate process control. During this stage of development, release/stability acceptance criteria is established and set. For process impurities (such as HCP and residual DNA) if the mechanisms/process of removal are well understood and if robust and consistent process capability is demonstrated (example through spiking studies), control through release testing and specification limits may not be necessary.

For **Phase II** products/clinical trials, the analytical methods are further optimized/qualified, lot release criteria are further refined, and validation acceptance criteria and assay parameters are set.

For **Phase III** products/clinical trials, full assay/test method validation is strongly recommended. FDA requires validated assays for registration-enabling clinical trials.

Post-licensure, the assays are monitored for trending analysis, and reviewed for performance and any test method replacements that indicate an improvement over the existing assay methods are considered.

As manufacturing changes or improvements get implemented in the late-stage development of biologics (for Phase II and III), analytical tests or specifications may be revised or added, or may be eliminated with appropriate justification. Additional improvements in the CQAs through the product life cycle will further help refine and optimize the TPP for product quality and help ensure the safety and efficacy of the defined product.

Resources:
FDA: Q8(R2) Pharmaceutical Development
FDA: Q8, Q9, & Q10 Points to Consider, Questions and Answers from Training Sessions
FDA: M4Q: The CTD—Quality
FDA: Analytical Procedures and Methods Validation for Drugs and Biologics
FDA: Points to Consider in the Manufacture and Testing of Monoclonal Antibody Products for Human Use
Article: Critical Quality Attributes: Assessment and Testing Strategy for Biotherapeutics Development

8.4 Stability Data and Shelf-Life Claims

Biological products change as they age in storage, but they are stable if their characteristics remain within the specifications. The shelf life is the number of days, months, or years the biologic remains stable at the recommended storage conditions. The experimental protocols commonly used for data collection that serves as the basis for estimating shelf life are called stability tests. The stress and accelerated stability studies used during development are not surrogates for real-time stability studies at licensure. The considerations for stability data and shelf-life claims are similar for small molecule drugs and biologics. For a more complete discussion of stability data and shelf-life claims, please refer to Section 6.4 of the Regulatory Knowledge Guide for Small Molecules. Also, see Section 6.4 of this guide for more information on biological product stability.

In the event of a stability testing failure for a manufactured batch (**out of specification** results in comparison with the reference standard), the CoA cannot be issued, and the product cannot be released. An investigation will be conducted to identify the root cause analysis of the results (if it is an aberration of the assay/testing process, personnel handling, or sample related) and resolve the problem before proceeding to make a new batch or product release.

Biologic-Specific Considerations

Biological products are unique. Both the sensitivity and stability of biological products—unlike small molecules—may require additional precautions.

- Stress and accelerated studies during development should demonstrate that the biological product is not prone to significant degradation or changes during a stipulated time frame (for example, three months). You may also have to demonstrate data from stress and accelerated studies showing that there is no impact of production scale on biologic DS and DP physicochemical stability, and that sterility and container closure integrity are maintained.
- Depending on the phase appropriateness, the stability methods need to be more rigorously approved/qualified or validated and meet ICH standards (validated methods typically required for Phase II and Phase III clinical products). If the final cGMP testing facility is different, appropriate method transfer, revalidation, or verification activities should be carried out and documented appropriately.
- The shelf life may be product class specific, and the duration of data required should be suitable to maintain the biologic DP in the supply chain and for patient availability given the long lead-time for production.

Resources:
CFR: 21 CFR 211.166 Stability Testing
FDA: Stability requirements for Phase 2 and Phase 3 INDs
FDA: Expiration Dating and Stability Testing for Human Drug Products
EMA: Topic Q5 C: Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products

8.5 Biologic Product Labeling and Packaging

cGMP compliance extends to labeling and packaging of DPs—both during development and post-licensure. For a more complete discussion of labeling and packaging, please refer to Section 6.5 of the Regulatory Knowledge Guide for Small Molecules.

Biologic-Specific Considerations

Biologics and biologically derived products require considerably different forms of labeling and packaging (vial labels, primary packaging, and secondary packaging) compared to traditional small molecule medicines.

Ensuring minimal exposure to environmental factors that can affect the integrity and efficacy of a biological product is a top priority. Changes in temperature or orientation during transportation, storage, and usage can affect these products but can be mitigated through appropriate packaging. In addition, packaging considerations involve understanding where bulk and clinical batches are manufactured and the location of clinical trial sites where the material will be shipped. The innovator and the contract manufacturer need to establish the best possible scenario to maintain, preserve, and monitor the supply chain of the product.

Resources:
CFR: 21CFR 211 Subpart G
FDA: Labeling for CBER-Regulated Products
FDA: Container Closure Systems for Packaging of Human Drugs and Biologics
FDA: SOPP 8412: Review of Product Labeling
FDA: Current Good Manufacturing Practices: Control of Components and Drug Product Containers and Closures
FDA: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use
WHO: Guidelines on Packaging for Pharmaceutical Products
U.S. Pharmacopeia: <1079> Good Storage and Shipping Practices
U.S. Pharmacopeia: <659> Packaging and Storage Requirements

8.6 Protecting the Integrity of Biologic Products

Certain biologics can be more sensitive to external factors and process unit operations. Post-manufacturing, formulation, and fill-finish operations should ensure that the biological product integrity and CQA (identity, purity, potency, stability, and performance) are retained during these processes. Special processes and procedures (such as aseptic fill-finish, storage, and container closure) may be required to ensure product integrity during fill-finish and related manufacturing operations.

Biologic-Specific Considerations

- **Handling of sensitive biologic products, inspection of clear and opaque suspensions, and inspection of amber vials distinguishing between foreign and product-related particulates can create some challenges for fill-finish operators.**
- **Simulation of the aseptic fill-finish process with mock media fill runs should be conducted to understand process performance (and not be surprised later).**
- **Ensuring accurate sizing of filters for sterile filtration is important to reduce hold-up and loss of high-value biologic products.**
- **In both sterile filtration and container closure filling unit operations, peristaltic pumps have become the standard for most biologics filling processes. For example, highly concentrated mAb or adjuvanted vaccine solutions can create viscosity and/or particulate based challenges in drug product fill–finish operations. Pumping viscous or particulate solutions through small-diameter tubing can generate shearing and other effects that could degrade the biologics. Tubing quality and hardness, diameters, and configurations need to be carefully evaluated prior to fill-finish operations which often helps manufacturers handle such variabilities.**
- **Interactions with the packaging material and containers should be evaluated as they can also cause change in the biological product (aggregation, sticking to surface) or introduce contamination by leaching compounds in the drug product. Studies that can help mitigate the risk to the product should be considered.**

Resources:
FDA: Sterile Drug Products Produced by Aseptic Processing
FDA: Container Closure Systems for Packaging of Human Drugs and Biologics
FDA: Container and Closure System Integrity Testing In lieu of Sterility Testing as a Component of the Stability Protocol for Sterile Products
FDA: Presentation: Aseptic Processing of Biological Products: Current Regulatory Issues
Pharmaceutical Inspection Convention: Recommendation on Validation of Aseptic Process

9 Market Authorization Application Submission

Most of the requirements and guidelines for submitting a Market Authorization application for new small molecule drugs and biologic drugs are the same. For a more complete discussion of application submission, please refer to Section 7 of the Regulatory Knowledge Guide for Small Molecules.

Biologic-Specific Considerations

Prior to marketing, biologics must be approved by a regulatory authority—in the U.S. this is FDA (see CBERs development and approval process description and biologics regulatory information). Within FDA, some

biological products are regulated by CDER while others are regulated by CBER.

FDA approval involves many steps, from the submission (and allowance) of an IND application through clinical trials (Phases I through III), to a request for **Biologics License Application** (BLA).

The IND provides FDA with assurance the innovator understands the health condition they are seeking to address, and that the proposed treatment:

- Can be manufactured consistently
- Does not have any obvious safety concerns that pose greater risk than the health condition itself
- Has minimal initial planned human exposure that is appropriate to the level of risk of the health condition

Changes in manufacturing processes or facilities may require bridging studies to demonstrate product equivalence pre- and post-change implementation.

Resources:

NIH SEED: CBER Small Business Support – Manufacturers Assistance and Technical Training Branch
NIH SEED: Basics of Interactions with FDA (CDER/CBER)

9.1 End-of-Phase 2 Meeting with FDA

Following your Phase II clinical trials, you will need to review and obtain an agreement from the FDA on the study designs for Phase III, which is the purpose of the End-of-Phase 2 (EOP2) meeting with the FDA. At this meeting, you'll need to effectively present the Phase III and submission strategy and confirm alignment with the FDA before the start of Phase III.

FDA will determine whether proceeding to Phase III is safe at this meeting. In addition, they will evaluate the Phase III plans and protocols along with your existing studies (especially dose estimation and dose selection to use in late-stage efficacy trials) to assess effectiveness and note if any additional information is necessary to support the marketing application. In addition, where novel trial designs are a possibility, their utility and applicability could be discussed at an EOP2 meeting. The EOP2 meeting is a critical milestone in the development program, so it's essential to prepare well.

In addition to the standard items required for all drugs, the EOP2 meeting for biological products also includes specific CMC topics for conventional biologics and rDNA protein biotechnology drugs.

A follow-up meeting may be warranted if new issues arise during Phase III studies that affect the drug development program. For example, the session can address significant changes in plans from those previously discussed in the EOP2 meeting or resolve potential problems and/or refuse-to-file issues.

The guidelines for requesting meetings with FDA are the same for new small molecule drugs and biologics. For a more complete discussion of the guidelines, please refer to Section 7.1 of the Regulatory Knowledge Guide for Small Molecules.

9.2 Biologic Manufacturing Process

The manufacturing process for biological products is more complicated than for small molecules due in part to genetic variability in the source material. Because of this, your BLA must contain a thorough description of product development, relevant manufacturing procedures, and all steps taken to ensure that the final biological product performs consistently across batches. For a more complete discussion of the guidelines, please refer to Section 7.2 of the Regulatory Knowledge Guide for Small Molecules.

Biologic-Specific Considerations

While BLAs and small molecule New Drug Applications (NDAs) serve the same purpose of gaining approval to market a drug in the U.S., they differ somewhat in terms of their application content and submission requirements. NDAs must establish that manufacturing methods preserve the drug's identity, strength, quality, and purity. Similarly, the contents of a BLA should show that the biological product is safe and potent; however, because biologics are obtained from living material, your BLA content must also demonstrate purity—particularly in terms of showing that the final product does not contain extraneous material. All biological product approvals occur through a BLA.

Because of the complexities of manufacturing biological products, a pre-license inspection of the facility is generally required before a BLA is approved. Once a BLA is approved, you are granted a license for the biological product, which permits its introduction into interstate commerce per Section 351 of the Public Health Service Act.

Most BLA submissions are assigned to CBER; however, BLAs for specific biological product categories are reviewed by CDER instead. These product categories include mAbs for *in vivo* use, most proteins for therapeutic use (e.g., cytokines, enzymes, and other novel proteins except those assigned to CBER, such as vaccines and blood products), immunomodulators, and growth factors.

For more information, refer to Section 8: Market Scale Manufacturing in this guide.

Resources:
FDA: Developing and Manufacturing Drugs Including Biologics
FDA: CMC and GMP Guidance
FDA: Determining when Pre-License/Pre-Approval Inspections Are Necessary
FDA: Pre-Approval Inspections Program
FDA: Frequently Asked Questions About Therapeutic Biological Products
FDA: Development and Approval Process
FDA: Guidance Biologics Compliance and Regulatory Information

9.3 Clinical Endpoints

An endpoint is a primary outcome measured by a clinical trial. The specific endpoint chosen for a given study has to do with clinical trial design, the nature of the condition being treated, and the expected effect of the experimental therapy being tested.

A clinical trial could use a clinical or a **surrogate endpoint**. A clinical endpoint is an outcome that represents a direct clinical benefit such as survival, decreased pain, or the absence of disease. A surrogate endpoint is a

substitute for a clinical endpoint used in trials where a clinical endpoint might not be possible or practical (if, for example, a drug's direct benefits would take several years to measure). Unlike clinical endpoints, surrogate endpoints do not represent direct clinical benefit but instead predict clinical benefit. Some surrogates are said to be "validated" or "established," meaning they have been proven to predict clinical benefit. Other surrogates have not been validated but are "reasonably likely" to predict clinical benefits. This latter type of surrogate is the basis of the FDA's accelerated approval pathway.

The requirements and guidelines for clinical endpoints for new small molecule drugs and biologic drugs are very similar. For a more complete discussion of clinical endpoints, please refer to Section 7.3 of the Regulatory Knowledge Guide for Small Molecules.

Resource:
FDA: Surrogate Endpoint Resources for Drug and Biologic Development

9.4 Regulatory Affairs

Filing a BLA for FDA approval is a substantial undertaking. Having an experienced regulatory professional lead this effort is important. If you do not have a regulatory expert on staff, it is important to engage a respected and appropriately qualified regulatory consultant with diverse subject matter expertise (clinical, preclinical, biostatistics, manufacturing, etc.) to support the filing.

For a more complete discussion about securing additional regulatory support for your application, please refer to Section 7.4 of the Regulatory Knowledge Guide for Small Molecules.

9.5 Proprietary (Brand) Names for New Biologics

FDA's guidelines on choosing a proprietary name for new drugs—both small molecule drugs and biologics—are very similar. The primary difference is there are additional requirements for four-letter suffixes in the nonproprietary name of a biologic. One purpose of the suffix is to enable tracking of separate products (originator biological products, related biological products, and biosimilar products) for pharmacovigilance (i.e., to inform adverse event reporting and assessment). More information can be found in FDA's Nonproprietary Naming of Biological Products.

For a more complete discussion of the naming guidelines, please refer to Section 7.5 of the Regulatory Knowledge Guide for Small Molecules.

9.6 Pre-BLA Meeting with FDA

Prior to submitting a BLA for FDA marketing approval, a **pre-BLA meeting** with FDA is strongly recommended. The guidelines for preparing for and requesting this type of pre-submission meeting is covered in Section 7.6 of the Regulatory Knowledge Guide for Small Molecules.

10 Expanded Use of an Existing FDA-Approved Biologic

The requirements and guidelines for expanded use of an existing FDA-approved product are similar for small molecule and biologic drugs. For a more complete discussion of expanded use, please refer to Section 8 of the Regulatory Knowledge Guide for Small Molecules.

Currently marketed biologics may enter the NIH funding stream by exploring indications outside currently approved label claims, expanding the biologic to diseases with similar metabolic pathways or mechanisms of action, or expanding to additional populations (pediatric or geriatric, pregnant women, predefined co-morbidities, etc.).

10.1 Biologic Repurposing

Expansion of approved biologics to new disease modalities and patient populations will depend on disease pathology at the molecular and cellular levels. Acceptability of using a biologic in a new patient population may be impacted by:

- Route of administration
- Dose selection
- Dose frequency
- Safety risks across different populations
- Improvement (**clinical outcome**, quality of life, etc.) over existing standard of care

FDA may require additional monitoring of product safety and statistical outcomes when expanding the patient population.

The requirements and guidelines for repurposing small molecule drugs and biologic drugs are similar. For a more complete discussion of repurposing, please refer to Section 8.1 of the Regulatory Knowledge Guide for Small Molecules.

Biologic-Specific Considerations

Determine early if you can access the biological drug either due to a lack of active patents and exclusivity, or through a licensing agreement with the original patent owner. The 505(b)(2) pathway can be used to obtain approval of certain follow-on biologics. The 505(b)(2) pathway, while largely used to obtain approval of small molecule drugs, is available for a relatively narrow category of biologics—specifically, those that had been approved under an NDA before the Biologics Price Competition and Innovation Act was signed into law. It is available only for that small segment of biologics. For example, a follow-on insulin product, not as a biosimilar, can be considered for NDAs under the 505(b)(2) pathway.

In general, for a 505(b)(2) product, the clinical trial materials for Phase I studies (often demonstrations of clinical bioequivalence) must be representative of the commercial manufacturing process, including packaging. In addition, the 505(b)(2) pathway allows the applicant to rely on the safety and effectiveness data of a previously approved product (see § 7002(e) of the Affordable Care Act). For the biologics that fit into this category, the 505(b)(2) pathway offers a pathway for marketing approval for certain biologicals products as biosimilars.

In the U.S., biological products are subject to a different premarket pathway and differing intellectual property (IP) protections than products regulated only as drugs. While a biological product must be licensed under a BLA establishing that it is “safe, pure, and potent,” an innovator of a non-biologic drug submits an NDA demonstrating the safety and effectiveness of the drug. For biologics, safety, effectiveness, and quality continue to be closely monitored even after regulatory approval. Certain new biological products receive twelve years of IP protection, while new drugs receive up to five years of IP protection. This differs because the IP for a small molecule drug might be adequately captured by a chemical compound alone while the technology for a biologic is a critical part of the production process. The legislation also provides different schemes for resolving patent issues regarding the entry of follow-on products for biologics and drugs.

Resources:
FDA: CDER BLA Information
FDA: CBER BLA Process Information

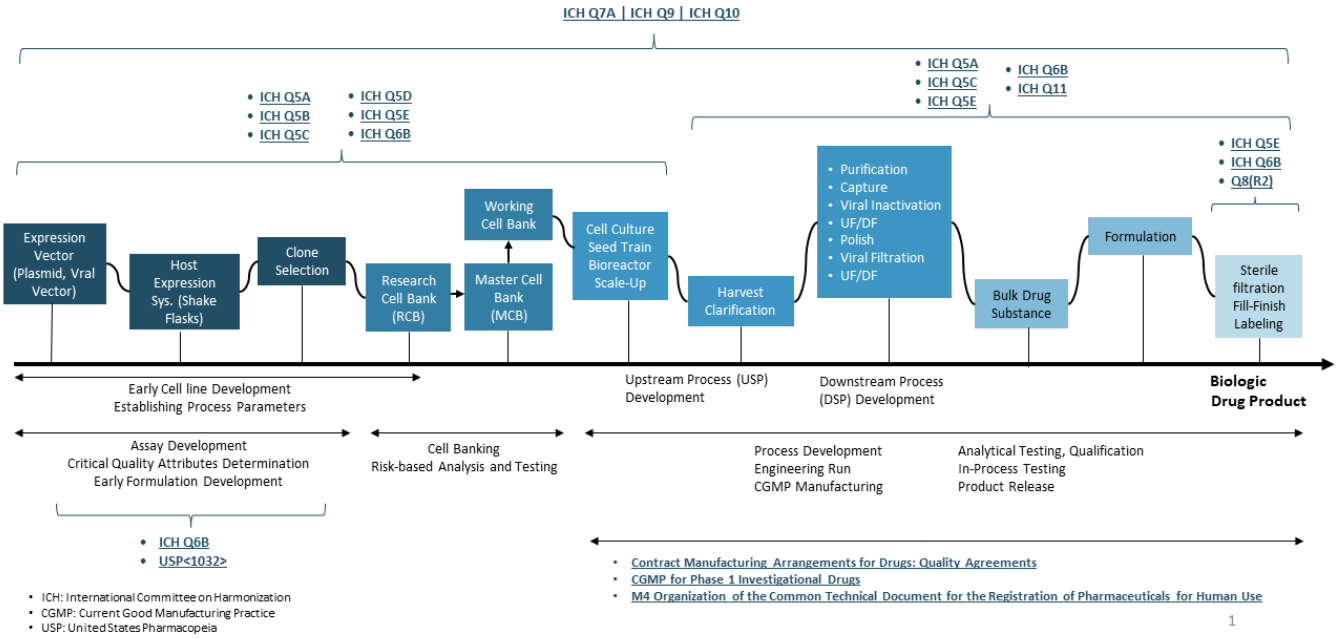
10.2 Bringing a Foreign Biologic to Market in the U.S.

Guidance is available for industry that describes procedures drug manufacturers need to follow to facilitate importation of prescription drugs, including biological products, that are FDA-approved, manufactured abroad, authorized for sale in any foreign country, and originally intended for sale in that foreign country. For a more complete discussion of marketing foreign drugs, please refer to Section 8.2 of the Regulatory Knowledge Guide for Small Molecules.

Resource:
FDA: Importation of Drugs Originally Intended for Foreign Markets

Updated November 2023

High-Level Biologics Manufacturing Process Flow Diagram With Appropriate ICH Guidance



- ICH: International Committee on Harmonization
- CGMP: Current Good Manufacturing Practice
- USP: United States Pharmacopeia

- Contract Manufacturing Arrangements for Drugs: Quality Agreements
- CGMP for Phase 1 Investigational Drugs
- M4 Organization of the Common Technical Document for the Registration of Pharmaceuticals for Human Use