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Regulatory Knowledge Guide for Small Molecules

NIH SEED Innovator Support Team

Introduction

Drugs—things we apply to or ingest in our bodies that are not considered food products and 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 prescription and over-the-counter, small molecule, and biological drugs.

This guide will help you better understand small molecule drug product development and the regulatory lifecycle. Small molecule drugs are generally organic compounds with a molecular weight around or below 900 Daltons. These molecules can be chemically synthesized or isolated from natural products (plants, animals, minerals, etc.). Small molecule drugs differ from biologic drugs (proteins, nucleic acids, cell therapies, etc.), as biologic drugs are typically highly complex molecules or cells derived from living organisms. However, the regulatory paths for small molecule and biological drugs have many similarities and significant differences. Please refer to the Regulatory Knowledge Guide for Biological Products for information specific to biological products.

Most small molecule drugs are designed to be taken orally (tablets, capsules, liquids, etc.). However, they can also be formulated as injectables (subcutaneous, intramuscular, intravenous, etc.), topicals (creams, lotions, gels, drops, suppositories, etc.), and aerosols (inhalants). In addition, small molecule drugs are often part of a "class" of similar molecules such as statins, steroids, nonsteroidal drugs, lipase inhibitors, macrolides, heterocycles, natural products, carbohydrate-based drugs, peptides, or oligonucleotides.

Small molecule drugs are generally organic compounds with a molecular weight of fewer than 900 Daltons. While most small molecule drugs are designed to be taken orally, they can also be an injection, topical, or aerosol.

The FDA's Center for Drug Evaluation and Research (CDER) is responsible for reviewing and approving small molecule drug development and monitoring safety post approval. During development, FDA reviews the information you provide describing the drug's quality, safety, and ability to provide health benefits that outweigh the risk of harm to the intended population.

Drug development and approval is a structured process within CDER and includes analysis of the target condition and available standard of care treatments (e.g., is the drug an improvement over the current standard of care methods), assessment of benefits and risks, and risk management considerations. This process is interactive and includes opportunities for you to meet with regulators during drug development, testing, and manufacturing.

Link to Small Molecule Drug 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 small molecule drug development process, the NIH Office of Extramural Research (OER), Small Business Education and Entrepreneurial Development (SEED) team recommends contacting the Enhanced Communication | FDA or the SEED Innovator Support Team.

After reading this Regulatory Knowledge Guide, you will better understand small molecule drug product development and the regulatory lifecycle. Specific topics that will be described include those listed below:

- How to ensure the final drug product maintains the active pharmaceutical ingredient's molecular properties, structural characteristics, and performance.
- How to use Investigational New Drug (IND)-enabling animal studies to demonstrate dose scaling and tolerance, safety, and efficacy of the drug product for the intended use before the first-in-human clinical trial.
- Best practices for product development and phase-appropriate manufacturing processes to achieve suitable product quality and safety profiles for Phase I trials and beyond.
- How to align chemistry manufacturing and controls development with phase-appropriate quality management system development to meet FDA expectations.
- Understanding key considerations when evaluating core competencies of contract manufacturing organizations and their fit for your product development.
- Benefits of initiating early FDA conversations and clearly understanding the regulatory requirements for the proposed drug product.

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1 Pre-Regulatory Phase Activities

This Regulatory Knowledge Guide for Small Molecules covers drug development Investigational New Drug (IND)-enabling studies through Market Authorization and drug repurposing. The pre-regulatory phase activities of discovery, translation, and early-stage development are addressed in a separate guide because the regulatory connection is indirect. These activities include those listed below:

- Defining the drug candidate and pre-animal testing
- Optimizing the synthesis of the drug candidate
- Early manufacturing requirements
- Conducting studies in small animals

An overview of the pre-regulatory activities is covered in the separate guide and a general timeline for pharmaceutical drug development are shown in Figure 1**.**

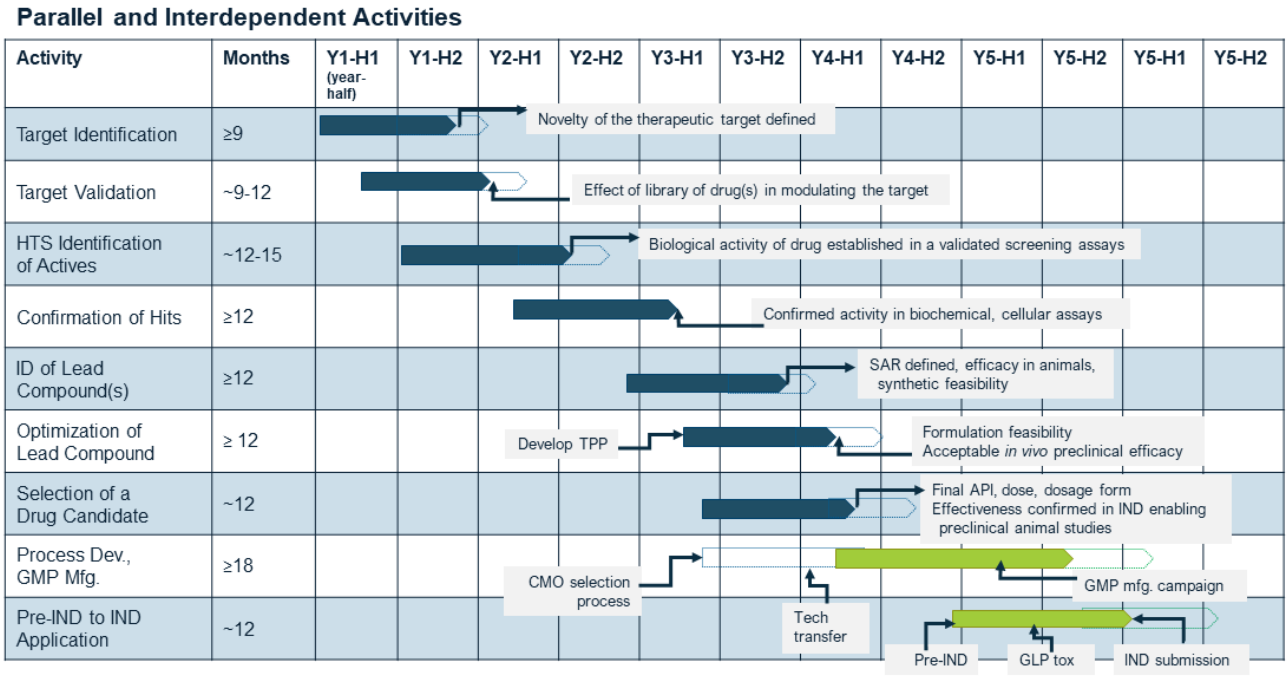
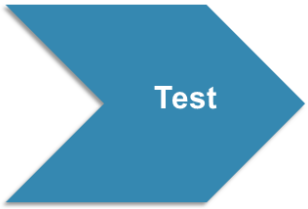


Figure 1. Estimated timeline for pre-regulatory activities in pharmaceutical drug development



2 IND-Enabling Studies

IND-enabling studies describe the pharmacology and toxicology studies performed in multiple animal species before the FDA allows human exposure to a new molecular entity. IND-enabling, non-clinical studies are typically conducted in small animals (rodents) and large animals (non-rodents), which may or may not be modified (genetically, physically, or

chemically) to mimic the target **indication**.

These studies aim 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.

Uses for IND-Enabling Studies

- **Justifying species selection for safety assessment**
- **Defining the starting dose regimen**
- **Defining the maximum tolerated dose**
- **Aligning and identifying the optimal and clinical route of administration**
- **Guiding human dose selection for initial clinical trials**

IND-enabling animal studies are generally conducted in a contract facility under current **Good Laboratory Practice** (GLP) and with complete documentation. These studies require an optimized drug formulation to be administered similarly before the anticipated first-in-human trial. Generally, this material has been manufactured during a pilot manufacturing run and meets the minimum acceptable **critical quality attributes** (CQAs) defined by the **innovator**. The non-clinical information collected in these studies informs pharmaceutical development programs at critical points by addressing important questions. The FDA expects an evaluation of the toxicological profile of the **drug product** in two species, rodents and non-rodents. For rodents, mice and rats are most frequently used. For non-rodents, dogs, minipigs, and monkeys are commonly used, although you will need to justify the species you select. The kind, duration, and scope of animal and other studies required to support an IND application will depend on the proposed clinical investigations.

If using mouse models, NIH encourages using public mouse repositories and sharing resources to promote reproducibility. Innovators can deposit their models in NIH repositories to be shared with other NIH awardees.

Note that new drugs and biologics aimed at preventing, diagnosing, or treating a rare condition (i.e., impacts fewer than 200,000 individuals in the U.S.) may be eligible for orphan drug designation (ODD). If you are seeking an ODD (which is separate from a marketing approval request), you should submit an ODD request to FDA prior to applying for an IND.

Resources:
FDA: Non-Clinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals
NIH SEED: Navigating FDA: Drug Development Requirements
NIH: ORIP: Mutant Mouse Centralized Repository for Researchers
NIH: Resources for Animal Models

2.1 Optimal and Consistent Production of Drug Product Formulation

A lead drug candidate should meet the following product-specific requirements: optimal formulation, CQAs; and effectiveness in *in vivo* animal studies and physicochemical, molecular, and functional *in vitro* and ***in silico*** assays. Once these attributes have been optimized, the proposed drug advances to testing in non-clinical, disease-indicating animal studies (*in vivo* models). The non-clinical studies should support the desired pharmacology, efficacy, and safety requirements for additional development. Figure 2 shows the range of drug product development activities that are undertaken to determine optimal drug production.

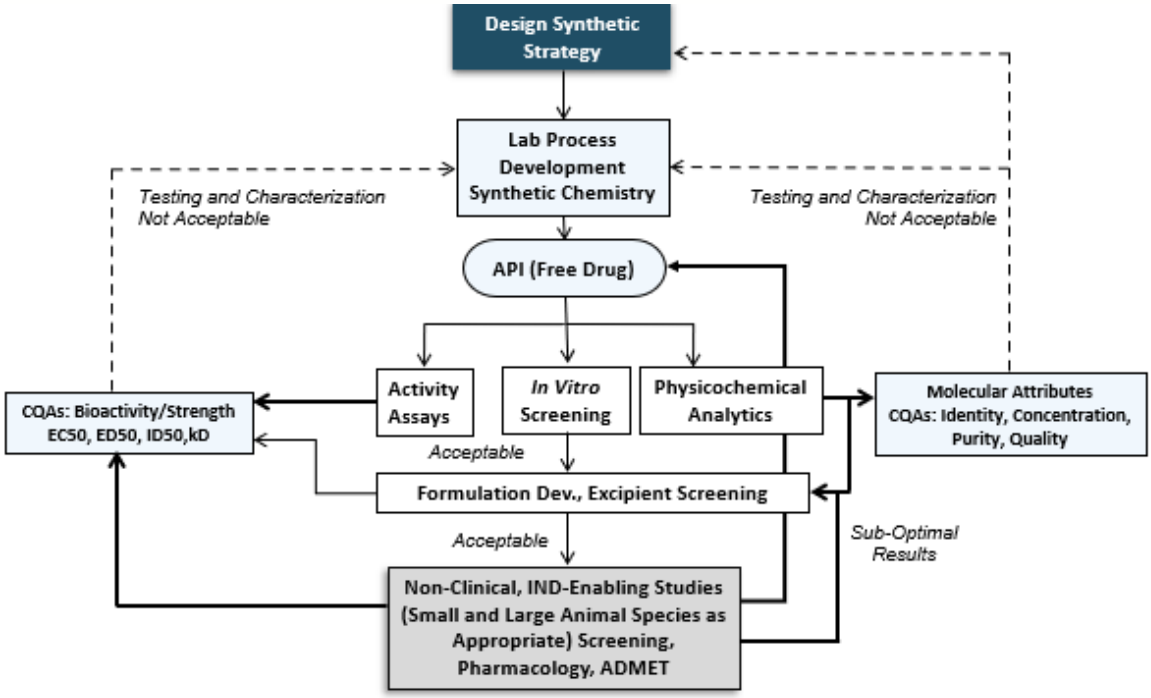


Figure 2. Development activities during pharmaceutical drug product evolution

Research scale process and product formulation production activities (usually made in smaller batches) should ensure that the product can be consistently produced following quality standards (batch-to-batch reproducibility). It is important to remember that as part of this work, the **drug substance** must be appropriately characterized and tested for compatibility with other components (**excipients**) in the final drug product.

2.2 Suitability and Dosing Regimen of Non-Clinical Large Animal Species

The selection of the appropriate large animal (e.g., non-rodent) model is based upon the ability of the model to predict the effectiveness and safety of the drug in humans. These studies enable comparison among different species and support understanding of the drug's effect on small animal species. It is vital for the animal model selected to inform the safety data for FDA. The animal model should replicate the human model as much as practical. If wild-type animal models are not appropriate,

genetically modified animals or humanized, transgenic animals may be used to validate drug-target interaction and drug activity in the target disease. Studies in large animals show the drug product's impact on the disease's pathogenesis and should be conducted with a drug product identical in dose and route of administration (ROA) to the planned first-in-human clinical trial. When developing your protocol for the large animal testing, be sure that your design creates an equivalent exposure with the small animal testing through allometric scaling.

In both cases (small and large animal studies), the physical and chemical properties of the drug, formulation, stability, residence time, and therapeutic modality should have the same attributes you intend for humans. Note that the expected first-in-human drug product should inform the drug dose-response and its effect on pharmacokinetics, pharmacodynamics, target receptor expression, metabolism, toxicity, and bioactivity/strength while determining optimal conditions for the new therapy.

NIH requires you to include a discussion of the proposed use and treatment of animals in the research design and methods section of funding applications, along with justification for the choice of species and number of animals to be used and validation of the Institutional Animal Care and Use Committee (IACUC) approval status for facilities conducting vertebrate research.

Resources:
FDA: S7A Safety Pharmacology Studies for Human Pharmaceuticals
EMA: Guideline on Strategies to Identify and Mitigate Risks for First-in-Human and Early Clinical Trials with Investigational Medicinal Products

2.3 GLP Toxicology Studies

GLP **toxicology studies** must be conducted before submitting the IND application. Toxicology studies are critical for defining/confirming the initial dose selection, regimen, and ROA and for predicting human safety parameters to be monitored throughout the clinical development program. Therefore, the study plan must be conducted with single and repeat-dose toxicity, genotoxicity, carcinogenicity, and other safety and pharmacological aspects of the final drug candidate.

Toxicology studies must be conducted with the same drug form used in clinical trials. The FDA has refused to allow clinical protocols to proceed when differences exist between preclinical study material and Phase I human use material.

The GLP **toxicology study**'s design and the experimental protocol's selection are defined on a case-by-case basis; they are tailored to the indication and responsiveness to the ROA and should provide enough information to evaluate the risks and safety of the candidate substance. Figure 3 illustrates the GLP toxicology studies that are required before submitting the IND application.

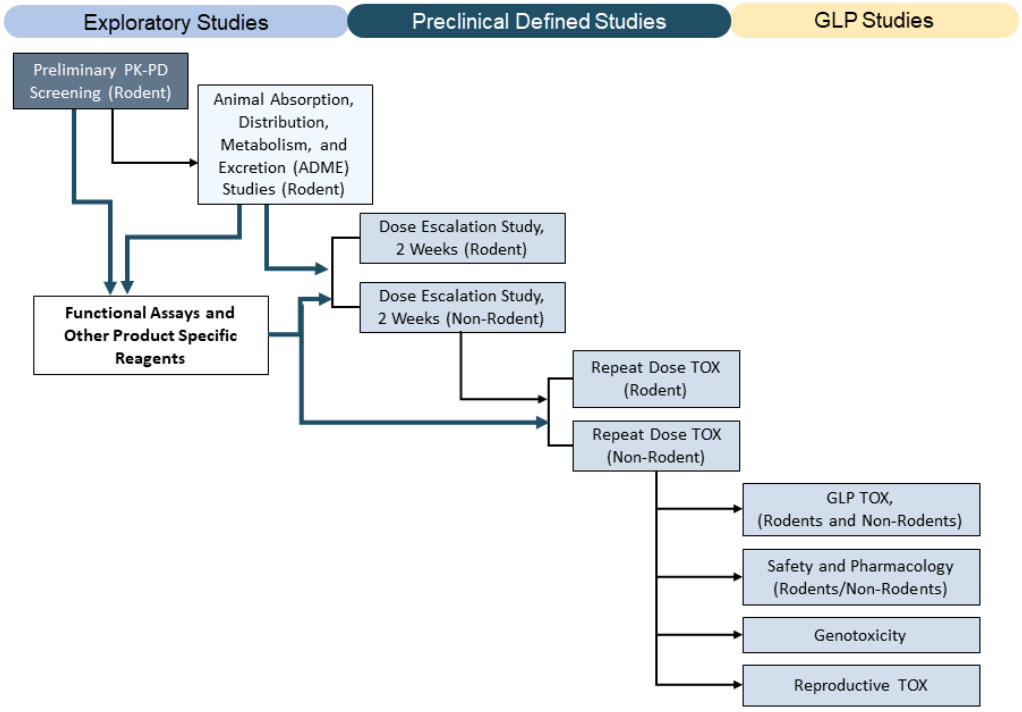


Figure 3. Types of studies required prior to submitting an IND

It is a best practice to connect with FDA before performing expensive studies of large animal species to confirm your data collection plan's approach, design, and strength. Receiving FDA input on the sufficiency of your studies on large animals may save both time and money in your total development program.

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

The resources listed below can guide you in performing the non-clinical safety studies required to open an IND for most drugs and some biologic drugs. For drug types such as oligonucleotides (siRNA) and peptides, which are chemically synthesized and can be highly animal species selective, knowing the pharmacological relevance of the toxicology species selected is critical. For these products, FDA has been mostly consistent with requirements, in line with those for small molecules.

As the regulatory framework continues to evolve for these specialized classes of products with more new product approvals (e.g., Onpattro® [patisiran], Ozempic® [semiglutide]), it is crucial to seek guidance from FDA (ideally in a formal meeting) on the feasibility, suitability, adequacy, and validity of appropriate study design, animal species/model, and non-animal testing methods before engaging in costly IND-enabling studies.

Resources:
FDA: ICH guidance on M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals
FDA: CDER New & Revised Draft Guidance for Various Product Categories
FDA: Pre-IND Consultation Program
FDA: Small Business Industry Assistance (SBIA) Learn
FDA: Small Business and Industry Assistance FAQs on the Pre-IND Meeting
EMA: ICH-S6R1 Preclinical Safety Evaluation Biotechnology Derived Pharmaceuticals
NIH SEED: Pre-IND Meetings

2.4 Contract Research Organization Selection for GLP Studies

FDA requires you to conduct GLP toxicology studies to evaluate the toxicity tolerance of small molecule drugs. The study protocols should follow guidelines recommended by the **International Council for Harmonisation** (ICH) or FDA. The resulting data will form the basis for proposing a preliminary therapeutic window, identify frequent drug safety concerns, and identify the highest safe dose when administered using the same formulation, by the same route, duration, and frequency as intended for the first-in-human **clinical trials**. A **contract research organization** (CRO) frequently conducts these studies—with complete oversight from an Institutional Animal Care and Use Committee (IACUC)—and maintains GLP documentation and uses validated **standard operating procedures**.

When you are evaluating CROs for IND-enabling animal studies, you should consider (at a minimum) the following factors about the facilities:

- Regulatory inspection history
- Experience with the applicable regulatory agencies (especially for multi-country clinical programs)
- Maturity of the facilities' **quality management system**
- Ability of a different facility to reconstruct the study
- Knowledge of and compliance with proper documentation and data analysis processes
- Experience with unique characteristics of the drug

Ideally, the CRO will assist you in designing the preclinical studies. Additionally, the CRO should support preparing regulatory documentation for pre-IND interactions and IND submission. The **common technical document** (CTD)—the basis of IND and marketing applications—includes chemistry manufacturing and controls information in Modules 2 and 4 (see FDA: Comprehensive list of IND application content and IND Application).

CRO GLP studies must be performed strictly according to good institutional scientific practices and meet GLP requirements to support FDA's IND requirements for Modules 2 and 4 (pharmacology and non-clinical studies).

GLP studies with the drug product must be conducted following 21 CFR Part 58 - GLP for Nonclinical Laboratory Studies, and the CRO must conduct the animal studies per 21 CFR Part 58, Subpart E–Testing Facilities Operation.

GLP studies are directly connected to the drug product. Therefore, any changes in drug product after IND-enabling studies are conducted may result in their needing to be performed again.

Any change in the drug product after conducting GLP studies may require a **bridging study** to demonstrate equivalency between the initial test and the new test. You and the CRO are responsible for ensuring all animals receive the correct drug product/test article dose during the entire study duration. Before initiating the study plan, confirm that the CRO has all the relevant product-specific information and placebos/controls. You may need to provide the necessary drug product and placebos/controls to the CRO and include this in your manufacturing plans.

Innovators should provide the CRO (at a minimum) with the following product-specific information:

- Lot and batch number of the drug product
- Certificate of analysis (or equivalent analysis documentation) of the drug product
- Dose ranges
- Solubility and stability information (if available)
- Formulation information (with the concentration of excipients)
- Storage information and labeled product
- Comparison of GLP toxicology material used to establish the preclinical data/studies

Resources:
FDA: M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals
FDA: S7A Safety Pharmacology Studies for Human Pharmaceuticals
NIH SEED: QMS for Small Molecule Therapeutics
NIH SEED: Contract Research Organization Checklist
NIH: Research Using Vertebrate Animals
NIH: Grants Policy Statement About Studies That Involve Animals
EMA: ICH-S6R1 Preclinical Safety Evaluation Biotechnology Derived Pharmaceuticals
HHS: Public Health Service Policy on Humane Care and Use of Laboratory Animals.

3 Pilot Scale Drug Manufacturing

Manufacturing a **pilot batch** of a drug product aims to demonstrate the scalability of processes, **unit operations**, and drug products by one magnitude and evaluate process consistency and reproducibility as scale increases. The material produced during pilot production should be comparable to the **reference standard** in specifications and quality attributes. Because it is process-informing, pilot-scale manufacturing is not generally performed under **current Good Manufacturing Practice** (cGMP) conditions.

The manufacturing site influences the size of the pilot scale run and where it is conducted, as well as process and technology complexity, the class of drug, and the technical expertise available. Robust processes facilitate **technology transfer** and enable the production of larger batches needed for clinical development and eventual commercial manufacturing.

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

Depending on the scale of the pilot batch, the material can be used to support 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.

3.1 Chemistry Manufacturing and Controls Plan Outline

A **chemistry manufacturing and controls** (CMC) plan describes a fully integrated development plan coordinating the sequential and parallel activities involved in optimizing and scaling up drug manufacturing and quality processes. Activities include drug product production, fill-finish and labeling, release, stability, and planning sufficient drug supply for non-clinical and clinical studies and commercial distribution. In addition, a complete plan should include key deliverables, success criteria, timelines, and cost estimates.

A phase appropriate quality management system should support chemistry, manufacturing, and controls in alignment and compliance with FDA expectations.

There are no specific templates or guidance documents describing best practices in CMC planning for new drugs. The unique characteristics, dosage form, indication, patient population, and other factors all contribute to the scale and requirements for each new drug.

Typical components of a CMC plan include those listed below:

- Critical quality attributes
- Scalability and cGMP manufacturing
- Fill and finish
- Formulation and analytical development
- Product release specifications
- Stability studies for drug substance and drug product
- Control strategy and critical process parameters
- Clinical trial material projections
- Storage and distribution
- Project management
- Raw material sourcing
- Quality management system development and regulatory documentation

Resources:
NIH SEED: Quality Management Systems for Small Molecule Therapeutics
Article: CMC Development Strategies for Small Pharma
Article: Drug Development CMC Considerations

3.2 Drug Candidate Characterization

Early development activities establish the physicochemical characteristics of the **active pharmaceutical ingredient** (API) and the formulated drug product. Therefore, analytical test methods should be robust and accurate and provide well-characterized, quantifiable information on the CQA of the API, drug substance**,** and drug product. The characterization will include structure identity (crystalline or polymorphic), counter ions (salts) and cocrystals, impurities, stability, appearance, solubility, and other chemical and physical properties. In addition, you need to document the physical and chemical equivalence of the drug product among batches used for critical activities such as stability, toxicology, and clinical trials.

Resources:
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: ICH Q6 Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products

3.3 Drug Product Quantity Needed to Support Early Development Work

There is no specific guidance regarding the quantity of material required for early development work; however, limitations in quantity can add challenges to foundational studies. You should develop a prioritized list of development activities, assess the amount of material needed for each, and allocate resources in alignment with this plan. For example, you can conduct material-sparing *in vitro* tests (a

battery of analytical and benchmarking testing) to optimize product formulation and use these results to predict the amount of material used later for *in vivo* animal studies. As you learn more about the new drug, improvements in the synthesis of intermediary and final product and purification practices will increase yields.

Early development work often involves significant changes in the proposed drug product's manufacturing, formulation, and analysis. These changes are a normal part of the development process. Demonstrating comparable activity as manufacturing processes mature is critical. Although developing the active drug is the focus, the simultaneous development of controls, or placebos is also essential and required for animal and human studies.

3.4 Contract Manufacturing Organization Selection

Choosing a **contract manufacturing organization** (CMO) to scale-up and produce preclinical and clinical-grade drug products is a significant partnering decision and can substantially impact the development program. Therefore, carefully evaluate CMOs to define some of the expectations and critical attributes needed to successfully scale-up the new product.

Before signing a contract, ensure the core competency of the CMO is a good fit for product development.

A CMO should have expertise in manufacturing process development and scale-up (ideally specific to the type of synthesis and formulation required for your product); however, knowledge and price are not the only aspects to consider. Additional activities a CMO typically provides include assay development, process documentation and recording, raw material and vendor selection/approval process, on-site fill/finish and labeling capacity, regulatory documentation and meeting support, and responding to regulatory questions about manufacturing activities.

In the case of small molecule drugs, contract manufacturing can cover the outsourcing of all or only a part of the manufacturing process for a product. For example, you can engage multiple CMOs: one as an API manufacturer and another to formulate the API, package the final drug product, and perform release testing. Hiring a CMO is ultimately based on business requirements, funding available, and other strategic factors. See Appendix A: Guidance for Selecting a CMO and Outsourcing.

The FDA inspects manufacturing sites; therefore, it may have records on your CMO in the inspection classification database. These can help determine if the CMO follows applicable FDA laws and regulations.

Potential questions for prospective CMOs include those listed below:

- Will the CMO be able to meet your anticipated production timeline and scale?
- Does the CMO have a robust quality system in place?
- How often are machines and equipment inspected/calibrated, people trained, process documents reviewed, etc.?

- Is the quality department firewalled from the operations team?
- Can the CMO demonstrate validated documentation for common activities and processes? Do they have a corrective and preventative action program that has identified the root cause and corrected issues with prior clients?
- What is the typical operating capacity? If the manufacturing timeline changes, will that be possible, or do they maintain 100% capacity except for facility shutdown for cleaning?
- Who will be the primary project manager, and do they have sufficient experience?

4 Clinical Scale Manufacturing

The amount of drug required to support a clinical trial will vary throughout development. First-in-human trials require less material than pivotal (efficacy) studies. FDA provides some guidelines; for instance, the FDA Guidance for Industry: Immediate Release Solid Dosage Forms, Scale-Up, and Post-Approval Changes outlines the maximum allowable batch size as ten times the size of the pilot batch (often used to support both IND-enabling large animal and first-in-human studies).

For example, the following batch size comparison provides a perspective regarding the magnitude of scale at various stages. Consider the size of bench-scale = X:

- Lab Pilot Scale = 10X
- Clinical Scale (Phase I, II) = 100 – 1000X
- Commercial Scale (Phase III) ≥ 1000X

All materials used in clinical trials must be manufactured following cGMP. However, FDA expects you to improve your manufacturing processes 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.

The scale of production runs should consider the amount of material needed for human dosing and quality and stability testing and any reserve samples that might be required for comparative (bridging) studies as manufacturing processes and scales change throughout development.

Resources:
FDA: CGMP Batch and Lot Definitions
FDA: Current Good Manufacturing Practice for Phase I Investigational Drugs
FDA: Q&A on Current Good Manufacturing Practices for Drugs

4.1 Manufacturing Drug Product for Clinical Trials

The amount of drug product and ancillary material such as a placebo or comparator drug required for a given clinical trial is calculated based on available information such as target enrollment, anticipated maximum dosing, release testing requirements, quality reserves, etc. FDA recommends estimating production targets using a bottom-up calculation allowing for excess material production as a safety buffer for any challenges in production yield, repeat testing requirements, labeling, etc. There is no "correct" answer regarding how much drug product to manufacture.

cGMP ensures that products are consistently produced using optimized and controlled manufacturing processes. A cGMP facility maintains a robust set of written process documents, hires and trains staff appropriately, documents all activities as they occur, and conducts regular reviews of all activities, documenting discrepancies from standard processes and implementing remediation plans for any consistency issues identified. If you are planning on working with a CMO, ask for verification that their process documentation and discrepancy logs are current and that the personnel assigned to the project are appropriately qualified. The CMO often becomes a partner in optimizing the manufacturing processes and may develop release tests based upon initial research lab tests. CMO staff also frequently possess regulatory experience, contributing an expertise that would otherwise need to be either sourced externally or added to the company team.

If you are working with a CMO, verify that they can manufacture material as needed and provide supporting documentation for the planned clinical campaign. Quality information for all manufactured lots will be submitted with the IND, either in the initial filing or as an amendment to an open file.

Although **Phase I** trial material may be exempted from some aspects of cGMP, as mentioned in the introduction to this section, this exemption does not apply if the Phase I **investigational drug** has been used in **Phase II** or **Phase III** studies or if the drug has been lawfully marketed.

Resources:
Article: Management of Investigational Drug Products
Article: The 5 Pillars of Clinical Trial Material Management

4.2 Certificate of Analysis Parameters

A **certificate of analysis** (CoA) summarizes test results and CQAs for a drug product, starting, and interim materials (API, drug substance, excipients, etc.). The CoA provides confidence to consumers that the drug is compliant with preset criteria and specifications. This is one method FDA uses to monitor lot-to-lot and batch-to-batch equivalency for a given drug.

Product-specific CoA criteria are established early in development and are refined and finalized as innovators and regulators learn more about a new drug. CoAs validate the equivalence of physical, chemical, and quality attributes among all batches, linking material manufactured during clinical

studies (used for market approval) and material produced post-market approval. The initial data set provides a control for future products. In addition, it increases FDA confidence that the currently manufactured drug is sufficiently like (and therefore has a similar risk/benefit profile as) the material and data reviewed for original Market Authorization.

If you are establishing your first CoA, read FDA Q7A GMP Guidance for API, which describes CoA content (for the API and formulated drug product) as including at least the following information: product name, molecular formula, batch/lot number, manufacturer and product manufacturing date/date of release, product description, dosage form, and storage conditions.

Product Description Criteria in the CoA

- Appearance
- Concentration/content/strength (UV absorbance and/or HPLC-based method)
- Identity (molecular weight/mass spec)
- Quality (pH [if a solution], Osm [if a solution])
- Quantity and quality, purity (HPLC-based methods (IEX, RP), SDS PAGE – Qualitative); synthetic siRNA (quantitative PCR, Ribogreen)
- Activity/strength (ELISA or OCTET or SPR assay, cell-based assay)
- Compendial assays as appropriate
- Endotoxin levels (set specifications) – <USP85>
- Microbial limits – <USP 61>
- Excipient levels (if any)– HPLC-based impurity levels (organic or inorganic or leachable) see Q3B Impurities in New Drug Products and Residual Solvents
- Water content
- Sterility testing may be needed dependent on dosage form (mostly liquid suspensions)

Resources:
FDA: 21 CFR 211.84: Testing and Approval or Rejection of Components, Drug Product Containers, and closures
FDA: FD&C Act Chapter V: Drugs and Devices
EMA: ICH Q6 Test procedures and Acceptance Criteria for New Drug Substances and New Drug Products

4.3 Retaining Samples for Bridging Studies

Many process changes may be incorporated simultaneously during the transition from bench scale to technical manufacture, from technical to pilot scale, etc. However, it is essential to demonstrate that these changes have not altered the critical attributes that led to selecting the lead compound and established information about the drug's activity or strength and safety profile.

A bridging study demonstrates comparability between material that exhibited a given profile and new material manufactured or formulated differently. The original and eventual materials are not expected to be identical, simply comparable in critical characteristics. In addition, differences between original and eventual material may be evaluated for potential biological impact. Determination of comparability and bioequivalence can be based on a combination of physicochemical and biophysical analytical testing, biological assays, and, in some cases, non-clinical (animal) or clinical (human) data.

As you implement changes to the manufacturing processes, the reserve calculations should incorporate plans for excess material to respond to FDA requests for bridging studies.

FDA requires retention samples (sufficient to perform release testing twice [minus sterility and pyrogen testing]) for API and bulk drug product. This is needed for GLP and cGMP manufacturing, but retention samples do not need to be designated as GLP or cGMP; therefore, a single sample per lot is acceptable.

There are specific requirements for bioequivalence/bioavailability studies where samples may need to be retained at the study site as overage requirements to ensure the study is conducted without bias. Under these circumstances, you should consult a quality assurance expert to ensure compliance with current regulations.

Resources:
FDA: Handling and Retention of Bioavailability and Bioequivalence Testing Samples
FDA: Q7A GMP Guidance for API (Section VI and Section XI. G)
FDA: Guidance on 21CFR 211.170 Reserving Samples
FDA: Guidance on 21 CFR 320.38 Bioavailability and Bioequivalence Requirements

4.4 Real-Time and Accelerated Stability Data for Clinical Trials

Stability testing of cGMP manufactured API and drug product establishes the shelf life and recommended storage conditions for pharmaceutical products. **Real-time stability studies** are conducted at the product-specific recommended storage conditions and monitored until the product fails the specification. In addition, **accelerated stability testing** is conducted under conditions that stress the material's temperature, humidity, and pH level.

A stability testing plan includes testing and monitoring CQAs susceptible to change during storage that could affect the product's identity, purity, or safety.

To understand the stability profile of a new product, a risk-based approach looking at short-term stability for process development batches of API (1–2 weeks to 1–3 months) can be tested using a subset of release assays (e.g., identity, purity, quality, strength). The results of these studies can generate baseline data to inform the stability of the API.

Resources:

FDA: Q1A(R2) Stability Testing of New Drug Substances and Products
FDA: Q7A GMP Guidance for API

5 Initiating First-in-Human Clinical Trials

Clinical trials determine the drug's benefits and risks in humans. Before starting a clinical trial, you must submit an **IND application** unless the study meets the criteria for an IND exemption. An IND application includes—among other information—specific sections summarizing preclinical development, detailed manufacturing information, and clinical investigations.

The innovator who submits the IND is ultimately responsible for ensuring product safety and regulatory compliance.

If FDA determines the information in the IND application supports a reasonable expectation of safety for the first human exposure of the drug in a new population, then FDA allows the IND, and the first clinical trial can begin enrolling participants. FDA is required to provide feedback within 30 calendar days of receipt of an IND. If no response is received, the clinical trial is allowed to proceed. It is possible FDA will not provide a letter authorizing the trial at the 30-day mark. The study may proceed unless FDA sends notification that the IND has been put on clinical hold or not accepted.

Sometimes NIH-funded research explores uses for drugs already available on the market. In some cases, these clinical investigations may not require FDA oversight (filing an IND). For the research to be "IND exempt," it must meet the following requirements:

IND-Exempt Drug Trials Must Meet Five Requirements

- The investigation is not intended to be reported to FDA as a well-controlled study in support of a new indication, and there is no intent to use it to support any other significant change in the labeling of the drug.
- In the case of a prescription drug, the investigation is not intended to support a significant change in the advertising for the drug.
- The investigation does not involve a route of administration, dose, patient population, or other factors that significantly increase the risk (or decrease the acceptability of the risk) associated with the use of the drug product.
- The investigation is conducted in compliance with the requirements for review by an Institutional Review Board and the requirements for Informed Consent (21 CFR part 50).
- The investigation is not intended to promote or commercialize the drug product (requirements of § 312.7).

More information about IND requirements and exemptions can be found in Guidance for Clinical Investigators, Sponsors, and IRBs.

5.1 Partnering with a CRO for Clinical Trials

Innovators often engage clinical CROs for specialized expertise and to manage clinical trials. CROs help ensure data quality and regulatory compliance. They may also provide **Institutional Review Board** (IRB) and FDA filing support, site selection and activation, recruitment support, clinical monitoring, data management, trial logistics, biostatistics, pharmacovigilance, medical writing, and project management. You may transfer any obligations (except overall study oversight) to a CRO, which must be documented in a written agreement. Although specific duties may be transferred, you remain responsible for the general conduct of the clinical trial—which includes ensuring the CRO can perform its assigned tasks in compliance with FDA requirements. Therefore, evaluate the qualifications of multiple CROs and engage the one most qualified to support the development work.

Resources:
NIH SEED: Clinical Research Organization Checklist

5.2 Developing Clinical Protocols

Clinical protocols describe how a drug will be tested in humans to determine its safety profile and effectiveness in improving quality of life. In the early stages of clinical development, human exposure is limited in the number of participants and the dose provided. However, these parameters increase as more is learned about how the human body reacts to the new drug. Therefore, from the first human exposure, it is vital to plan what the risk profile looks like in a trial.

Clinical protocols should include descriptions and allowable ranges for all predictable outcomes—both beneficial and adverse. Studies may consist of **primary and secondary endpoints** and **surrogate endpoints** and must specify study eligibility criteria, sample sizes, dosing regimen, stopping rules, etc. Early human studies assess safety and tolerability, using designs such as **single ascending doses** (which evaluate the safe dose range) and **multiple ascending doses** (which assess **pharmacokinetics** and pharmacodynamics). Sometimes, these studies identify a **maximum tolerated dose**. These early, first-exposure studies will inform the next clinical stage—early efficacy studies enrolling patients with a target indication. In some (life-threatening) conditions, Phase I studies may be allowable in patients rather than healthy volunteers.

When the NIH Institutes and Centers (ICs) receive clinical research study plans within a grant proposal, the Clinical Terms of Award require that the clinical research study plan be documented in a consolidated format, including applicable elements following the ICH Guideline for Good Clinical Practice E6(R2). NIH recommends using a protocol template to ensure all applicable elements of ICH are included.

There are many NIH policies related to clinical trial conduct. Always check with your NIH program official if you have questions about the documentation or risk mitigation activities required for a clinical trial award.

5.3 Developing a Viable Accrual Plan for the Clinical Program

Recruitment and retention of a diverse group of participants for clinical trials are often challenging. Identifying, engaging, and retaining clinical sites where clinicians with enough patients exhibiting the drug's target condition is critical to accrual success. Therefore, propose a comprehensive and realistic plan to address recruitment and retention issues. Some considerations include these questions: is the number of planned sites appropriate, will the sites be able to meet accrual goals, and are additional sites or investigators available to join the team if needed?

In the case of rare disease drug development, you should attempt to coordinate with patient advocacy groups focused on the specific disease area to help identify clinicians and participants. Such organizations play an important role in helping investigators develop trials with clinical design and outcomes that are meaningful to the affected population.

You should also perform resource planning and risk assessment to identify potential risks that could affect the trial, data collection, or critical processes' performance. For example, additional risks can include insufficient staff at the site, personnel leaving the project, unsatisfactory compliance with patient diary requirements, and longer than anticipated regulatory approval.

Certain NIH ICs provide detailed information and organizational frameworks with requirements for study start-up through site initiation visits and site activation. Consult your funding IC for their guidance. NIH requires compliance with the Clinical Terms of Award as discussed in the Notice of Grant Award for grants and cooperative agreements that involve human subjects and meet the NIH definition of clinical research.

Resources:
FDA: CP 7348.811 for Clinical Investigators and Sponsor-Investigators
FDA: Bioresearch Monitoring for Sponsors, CROs, and Clinical Investigators
NIH: Clinical Trial Requirements for Grants and Contracts

5.4 Protocol Submission and IRB Approval

An IRB must also approve and periodically review clinical trials under an IND application. IRBs protect the rights and welfare of human research participants. The NIH holds the primary awardee responsible for ensuring that human subjects policy requirements have been met regardless of where the human subjects' activities are conducted. IRBs are responsible for ensuring that all research protocols, informed consent documents, and related materials comply with human subjects' research regulation through the initial review. See the U.S. Health and Human Services (HHS) regulation 45 CFR 46.118, 46.119, 46.120, 46.122, and 46.123, for details on materials reviewed. IRBs also perform annual reviews of protocols if required by 45 CFR 46.109 subpart e or other federal, state, or local regulations.

The NIH Grants Policy Statement requires submitted applications that include human subjects research to have IRB approval at submission or within 60 days after the application receipt date (see NIH Policy for IRB Review of Human Subjects Protocols in Grant Applications).

Innovator/awardee institutions and their affiliates engaged in human subjects research and IND-enabling studies that involve the use of human tissues or other samples must obtain a **Federalwide Assurance (FWA)** and follow Federal regulations and Office of Human Research Protections policies and guidance to establish appropriate policies and procedures for the protection of human subjects. In accepting an award that supports human subjects and human tissues research, the grantee institution assumes responsibility for all research conducted under the award, including the protection of human subjects at all participating and consortium sites. This includes ensuring that an FWA and certification of IRB review and approval exists for each site before starting research on human subjects.

Resources:
NIH: Clinical Trial Requirements for Grants and Contracts
NIH: Single IRB Policy for Multi-Site or Cooperative Research
HHS: FWA, OHRP and IRB FAQs

5.5 ClinicalTrials.gov Registration

NIH requires all clinical trials register in the National Library of Medicine (NLM) clinical trials database (ClinicalTrials.gov). The NLM assigns a National Clinical Trial Identifier Number when a new study is registered in the database. You are responsible for registering the clinical trial with NLM. The NIH policy requiring ClinicalTrials.gov registration for all funded clinical trials differs from the FDA regulation to register only Phase II and higher drug trials. Failure to register a Phase I trial may cause delays in award funding.

Resources:
NIH: Requirements for Registering & Reporting NIH-funded Clinical Trials in ClinicalTrials.gov
NIH: Clinical Trial Requirements for Grants and Contracts
NIH: Policy and Regulation on ClinicalTrials.gov Registration and Reporting

5.6 IND Submission and Approval

Before human testing can begin, investigators must submit an **IND application** with FDA (or an applicable Regulatory Health Agency). The IND summarizes the information known about the new drug based upon manufacturing and quality analysis and animal studies (preclinical evaluation). It includes the rationale for believing the new therapy will be effective in an initial clinical protocol—usually designed to assess initial safety of the new drug in healthy volunteers. Figure 4 shows the five modules of an IND.

A Successful IND Application Includes:

- A general investigational plan describing the overall approach to evaluating human response to the new drug
- An Investigator's Brochure describing the attributes of the new drug to clinicians who will lead the clinical trials
- Pharmacology and Toxicology information—non-clinical safety and efficacy data
- Manufacturing information—drug composition, manufacturing controls, stability, manufacturing processes, etc.
- Phase I clinical trial protocol—study design, testing plan, informed consent forms, investigator information, etc.

When FDA receives an IND application, it assigns an IND number for tracking all communications and activities related to the specific drug. The FDA has 30 days to review the application for safety concerns, after which the IND becomes effective and clinical trials can begin. However, there may not be an official communication from FDA allowing the new trial to start at the 30-day point.

If FDA has concerns about a clinical program (related to manufacturing, preclinical safety data, or clinical protocol design), it places a clinical hold on the proposed trial. FDA will always send an official communication when it puts a clinical program on hold.

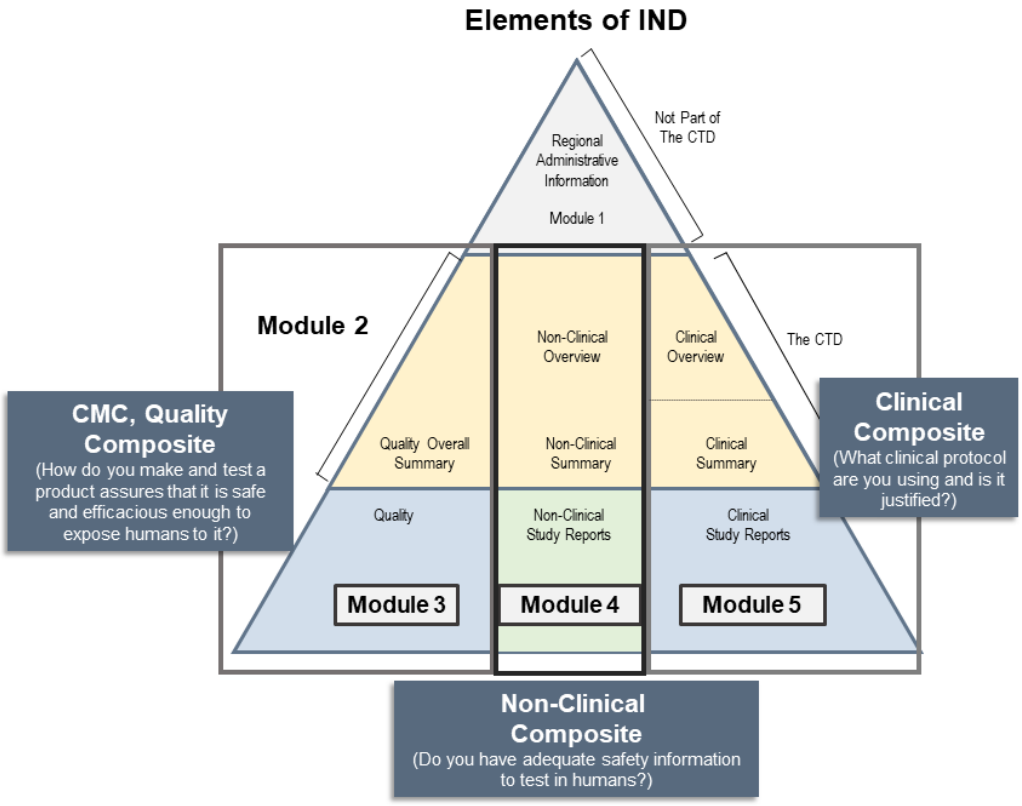


Figure 4. Main pillars of an IND application

5.7 Monitoring and Training of Clinical Trial Sites

All clinical investigators and clinical trial staff involved in the design, conduct, oversight, or management of clinical trials must be trained in **good clinical practice** (GCP) guidelines. The guidelines help ensure clinical trials' safety, integrity, and quality by addressing elements related to their design, conduct, and reporting. Site monitoring is tailored to each investigation—there is no one-size fits all approach.

Effective clinical investigation monitoring oversees the progress of the clinical trial, supports the conduct, collection, and recording of complete and accurate clinical trial data, and supports compliance with the study protocol, standard operating procedures, and GCP regulations—thereby protecting the human research participants.

It is a best practice to use a risk management approach in the design of clinical trials and propose monitoring tailored to the specific human subject protection and data integrity risks of the trial. The monitoring plan should identify intended methods for monitoring (e.g., on-site monitoring, remote or centralized monitoring, risk-based monitoring) and propose why this is the appropriate approach. You are responsible for ensuring trial participant safety, participant status, and trial data quality and integrity throughout (and sometimes post) the clinical trial—even if you transfer some or all responsibility for clinical trial operations to a CRO.

Resources:
EMA: Good Clinical Practices Guidelines

6 Market Scale Manufacturing

As a drug development effort progresses from discovery through early *in vitro* and animal testing, IND-enabling studies, first-in-human and follow-on clinical trials, and (hopefully) to the commercial market, the drug making process will change dramatically. Starting with the synthetic bench scale, a few milligrams or grams of pure API or the **bulk drug substance** may be produced for early animal studies. With preliminary formulation activity, the API can be formulated with the **excipients** and is referred to as the final drug product. When a drug is distributed for clinical trials, the API should be reproducibly produced using cGMP at a kilogram scale and formulated for optimal delivery as a final finished drug product. At the commercial stage, multi-kilogram batches are typical, and manufacturing may occur at multiple sites, even in various countries or continents, to support the medical needs of a national or global population.

CMOs often support scale-up activities, and different CMOs may support pre-IND manufacturing versus clinical or commercial scale production. In all cases, you should ensure the contracted CMO can meet production scale and timing. CMOs should also provide appropriate documentation to support regulatory filings.

Regulatory guidance documents clarify batch requirements; for instance, the FDA Guidance for Industry: Immediate release solid dosage forms, scale up, and post-approval changes outline the maximum allowable batch size as ten times the size of the pilot/bio batch. In addition, the FDA's cGMP guidance 21 Code of Federal Regulations 210.3 clarifies batch and lot definitions.

For example, the following batch size comparison provides a perspective regarding the magnitude of scale at various stages. Consider the size of bench scale = X:

- Lab Pilot Scale = 10X
- Clinical Scale (Phase I, II) = 100 – 1000 X
- Market Scale and Phase III ≥ 1000 X

6.1 CMO Manufacturing Guidelines

Innovators who use CMOs remain responsible for product quality, safety, efficacy, and **cGMP** compliance. Therefore, the selection of a CMO should be made with careful attention to the facility's record of compliance with regulations and strong manufacturing practices.

CMO Responsibilities

- **Maintain a good record of compliance with FDA inspections and audits**
- **Comply and adhere to chemistry manufacturing and controls practices of both internal quality systems and client-specific requirements**
- **Show qualified/validated processes for common activities (cleaning, training, raw material intake, equipment calibration, etc.)**
- **Employ sound overall quality management systems**
- **Demonstrate robust technical and engineering experience and competencies**
- **Have sufficient production scale capabilities**
- **Demonstrate strong overall company management**

Ensure the facility has experience with your specific product type (tablet, gelcap, extended-release coating, inhaled product, ointment, etc.) and that it can support the product lifecycle development throughout the immediate contract period—and potentially beyond.

Resources:
NIH SEED: An Innovator's Quick Start Guide to CMOs
NIH SEED: Innovator Checklist for Finding CMO
FDA: Contract Manufacturing and Quality Agreement
FDA: Guide to Inspections of Dosage From Drug Manufacturers

6.2 Manufacturing Batch Records

The **manufacturing batch record** (MBR) documents all quality attributes: information about raw materials, in-process control tests/values, and release tests/values that describe the manufacture of a drug. In addition, MBRs contain instructions describing step-by-step unit operations to be followed (and documented) during the manufacturing process. MBRs provide a reference point for identifying manufacturing issues, ensuring appropriate maintenance and cleaning of machinery, and supporting quality operations in a manufacturing facility.

21 CFR 111 Production and Process Controls; 21 CFR 211.186 Master Production and Control Records describes the requirements for batch record documentation.

FDA Q7A GMP Guidance for API provides the FDA's current thinking regarding the cGMP manufacture of APIs within a quality system. These guidelines are intended to increase the likelihood that each batch of material will meet the quality and purity characteristics you developed and that FDA reviewed and accepted. These practices extend beyond the manufacture of the API and include production and process controls, documentation, MBRs and review, packaging and labeling, validation, etc.

6.3 Drug Product Certificate of Analysis

A CoA summarizes test results and CQA for a drug product and the starting and interim materials (API, drug substance, excipients, etc.). The FDA also uses CoAs to monitor a drug's lot-to-lot and batch-to-batch equivalency.

Before finalizing the CoA criteria, you must establish and validate the analytical test methods for the product under development referenced in the CoA. These tests describe physicochemical and biophysical CQA of the API, drug substance, and drug product and compare to reference standards agreed upon with FDA. This testing is product-specific and typically includes, but is not limited to, information about identity, concentration, purity, in-process and other impurities, solubility, and strength of the drug product.

The FDA provides feedback on the draft CoA and chemistry, manufacturing, and controls criteria during development meetings (**pre-IND, End-of-Phase 1, End-of-Phase 2, pre-NDA/Biologics License Application meetings,** etc.).

If you are establishing your first CoA, read FDA Q7A GMP Guidance for API, which describes CoA content (for the API and formulated drug product) as including at least the following information: product name, molecular formula, batch/lot number, manufacturer and product manufacturing date/date of release, product description, dosage form, and storage conditions.

For more information on minimum product description criteria in the CoA, see Section 4.2 Certificate of Analysis Parameters.

Module 3 of an IND submission describes the quality attributes and **CMC** criteria for the drug substance and drug product. CTD Quality and CMC Module 3 guides the specific requirements for drug substance and drug product (including impurities) within the CTD that will form the basis of your IND submission. In addition, the following documents describe the types of supporting documentation required in drug applications.

Resources:
FDA: Manufacture of Drug Substances
FDA: Drug Substance Chemistry, Manufacturing, and Controls Information
FDA: Q3B(R2) Impurities in New Drug Products
FDA: ANDAs-Impurities-in-Drug-Products

6.4 Stability Data and Shelf-Life Claims

The shelf life of a drug is the term used to describe the period after the date of manufacture during which the drug product maintains its product specifications (purity, bioactivity or strength, and CQA) as described in the CoA if stored under recommended conditions. Shelf life is commonly estimated using real-time and accelerated stability tests during early development. In **real-time stability testing**, a product is stored at recommended storage conditions (e.g., frozen, refrigerated, room temperature, in the dark, desiccated) and tested for all CoA characteristics at regular intervals until it fails product specifications. In accelerated stability testing, a product is stored at elevated stress conditions (e.g., alternate temperatures and humidity).

ICH Q1A(R2) Stability Testing of New Drug Substances and Products and Q1E Evaluation of Stability Data describe recommended approaches for conducting stability studies for API, drug substance, and drug product and guide estimating actual stability from accelerated study data. The FDA does not allow the expiration date of a new drug based on the analysis of accelerated study samples. However, it is possible to update the expiration date for a drug under clinical development as new real-time stability data is obtained.

6.5 Drug Product Packaging and Labeling

cGMP compliance extends to packaging and labeling drug products during development and post-market. Labeling as defined by FDA applies to primary containers, cartons primary containers are placed in, and information provided as package inserts. Regardless of its form, labeling information must meet the FDA's written procedures, specifications, content, and review requirements.

Labeling must be accurate and summarize the essential scientific information for the end user's safe and effective drug use. For example, the labels should include the proprietary drug name, product strength and amount, route of administration, storage condition, warnings or cautionary statements (if any), manufacturer name, lot number, and expiration date.

7 Preparing for the Market Authorization Application Submission

The **Market Authorization** request for a small molecule drug is called a **New Drug Application** (NDA). An NDA contains a complete summary of the information about the drug organized into three primary sections: CMC, preclinical (animal) data, and human clinical data. Before submitting an NDA, a **pre-NDA meeting** with your FDA review team is helpful to confirm that the necessary development steps have been completed and the clinical, safety, and manufacturing data are adequate for approval (e.g., no additional studies are required, whether safe use requirements or post-market studies are necessary, and if an **Advisory Committee** meeting may be required).

The FDA may require additional risk assessments after Market Authorization to confirm the drug's long-term safety and efficacy, including its risks, benefits, and optimal use.

7.1 End-of-Phase 2 Meeting with FDA

Milestones in a drug development plan—such as completion of Phase II (early efficacy) trials—are excellent opportunities for you to meet with FDA to address important or outstanding issues.
The first of these meetings happens at the end of Phase II clinical trials. The **End-of-Phase 2** (EOP2) **meeting** is an important opportunity for the company to discuss clinical trial design (e.g., primary outcome definition, choice of comparator, power of the study) for its **Phase III** clinical trial program. The EOP2 meeting also allows the team to confirm that, if successful, the planned Phase III trials will support the FDA marketing approval application. For serious conditions (e.g., life-threatening or severely debilitating diseases) and some rare diseases, the EOP2 meeting may confirm that Phase III trials are not required for approval.

A vital aspect of the EOP2 meeting is gaining FDA agreement with the planned Phase III trials. A second key aspect is discussing CMC issues, including identifying potential impediments to growth from clinical to open market scale. The complete package for the EOP2 meeting is due at least 50 days before the meeting.

Resources:
FDA: IND Meetings for Human Drugs and Biologics
FDA: Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products
FDA: Expedited Programs for Serious Conditions–Drugs and Biologics
FDA: New Drug Application (NDA)

7.2 Drug Manufacturing Process

Before a drug can be marketed, you need to be manufacturing the drug at the appropriate (market) scale in a high-quality manner using cGMP.

Questions a Comprehensive Drug Manufacturing Development Plan Should Answer

- **Is the company or contract manufacturing organization plant capable of manufacturing the drug/dosage form following the FDA cGMP regulations?**
- **Has the drug product undergone modification (improved processing conditions, excipient use, packaging, etc.) during the evolution of the manufacturing process?**
- **Does the manufacturing process produce a consistent product?**
- **Does the manufacturing facility have a good history with FDA inspections?**
- **Does the stability data support the shelf-life claim?**
- **Do the in-process and final testing methods provide continued reasonable assurance of drug product identity, strength, quality, purity, safety, and effectiveness?**
- **Has the manufacturer validated its manufacturing and quality processes and demonstrated its conformance and reproducibility at scale?**
- **Does the labeling and packaging information indicate the drug's Intended Use and Directions for Use, and are packaging/labeling materials consistent with the format confirmed with the FDA (21CFR 211 Subpart G)?**

For more information, see Section 6, Market Scale Manufacturing.

7.3 Clinical Endpoints

Clinical endpoints are clinical trial results that demonstrate if a drug works in humans the way a developer thinks it will. Endpoints may be actual **clinical outcomes**, such as decreased number of myocardial infarctions (heart attacks) among the treated population. Alternatively, they may be **surrogate endpoints**, such as the prevalence of a biomarker (like LDL or "bad" cholesterol) —which are generally agreed to indicate the likelihood of having a heart attack. Note that clinical outcomes alone are not sufficient for market approval. You should also assess progress on other requirements, including any non-clinical studies and scaling and building quality systems around the drug manufacturing process

Scientifically valid evidence of effectiveness (reaching statistical significance for an actual or surrogate endpoint) is a crucial component of FDA's assessment of the benefit-risk profile for a new product or a new use for a current product. However, no therapy is without risk. Therefore, FDA uses a benefit-risk assessment to determine if a drug should be granted market access. Some of FDA's considerations include an evaluation of safety, how effective the drug is for its indication, the severity of the condition

the drug will treat, what (if any) therapies are currently available, and whether risk management tools are needed to ensure proper use of the new drug.

In most cases, you will need to conduct clinical trials to demonstrate substantial evidence of efficacy and safety. The primary clinical endpoints, which may be discussed with FDA in the **EOP2** meeting and specified in Phase III clinical trial protocols, must be met to demonstrate efficacy. The FDA summarizes general Clinical Trial expectations and requirements.

The FDA Guidance on Demonstrating substantial evidence of effectiveness for human drugs and biologics describes FDA's process for filing NDAs or applications for supplemental indications of already approved drugs. In some cases, such as a therapy for a virulent and lethal pathogen, conducting human clinical trials is impractical or unethical. In these cases, developers may use surrogate test systems and seek approval using the animal rule.

7.4 Regulatory Affairs

Filing the NDA for FDA approval is a substantial undertaking and having an experienced regulatory professional lead this effort is a priority. If you do not have a regulatory expert on staff, engaging a respected and appropriately qualified external team with diverse expertise (clinical, preclinical, biostatistics, manufacturing, etc.) is essential to support this filing.

Ideally, the regulatory professional leading the NDA submission will have been working with the team throughout (at a minimum) the Phase III development program—preferably longer. One regulatory professional does not need to create the total content of the submission. Instead, subject matter experts from multiple disciplines should contribute to the submission. If you use a team of experts, it is beneficial to designate a lead regulatory professional who can provide critical feedback on draft documents to ensure they will be acceptable to FDA.

7.5 Proprietary (Brand) Names for New Drugs

You are responsible for providing a shortlist of proposed names for the new drug to FDA. Without FDA concurrence, no "brand name" can be used for marketing (or other) purposes. However, FDA may conditionally accept a proprietary or brand name before the Phase III trials. This gives clinicians exposure to and awareness of emerging products in clinical trials and publications, potentially increasing post-approval adoption rates.

The choice of a proprietary name is essential. Names are how a drug will be identified and can help retain market share among healthcare professionals and consumers. The proprietary name approval request should be submitted as early as possible before submitting the NDA. FDA reviews the proposed names to prevent medical errors, including avoiding look-alike/sound-alike names or nomenclature that could confuse or mislead consumers or healthcare providers. FDA also considers whether the name could imply superiority or minimize risks of harm. When submitting a proprietary name, primary and alternate names pronunciation, derivation, intended meaning of modifiers, the

proposed name's pharmacologic/ therapeutic category and other information required by FDA should be included.

Resource:
FDA: Contents of a Complete Submission for the Evaluation of Proprietary Names

7.6 Pre-NDA Meeting with FDA

Milestones in a drug development plan—such as completion of Phase III (pivotal or efficacy) trials—are excellent opportunities to meet with FDA to address important or outstanding issues. Before submitting an NDA for FDA marketing approval, a pre-NDA meeting is an ideal place to review if all necessary steps have been completed and the anticipated data and analyses are adequate for approval of the new drug. This meeting may also indicate if an Advisory Committee meeting may be required for FDA to receive other expert opinions on the safety and efficacy of the new drug.

FDA strongly recommends a pre-NDA meeting before submitting an NDA (typically held three months before target NDA filing). During this meeting, you can obtain a general agreement with FDA about the sufficiency of the data to support FDA's review. Therefore, preparing straightforward draft questions and a pre-meeting briefing package is essential. The regulatory professional leading the NDA submission should lead the meeting, and all team members responsible for section development should help prepare questions and provide materials for the meeting briefing package. In addition, the regulatory lead can provide guidance on the overall strategy for the pre-NDA meeting, attend the meeting, and help the company understand how to address any concerns raised by FDA during the discussion.

Questions proposed during a pre-NDA meeting may include: Does the data support the proposed indication/labeling? Are the data and documentation requirements clear and comprehensive? Does FDA anticipate an Advisory Committee Meeting will be required?

Resources:
NIH SEED: Basics of Interactions with FDA
FDA: Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products
FDA: Questions to Ask FDA During Formal Meetings

8 Expanded Use of an Existing FDA-Approved Drug

If you plan to investigate a drug that has been partially developed or is available on the market, there are multiple approaches to gain access to the drug. If there are no patents, or if the patents are expired, you can synthesize/manufacture the drug. If patents still protect the drug, you may be able to execute a licensing agreement for the initial intellectual property or expansion of the intellectual property for an indication outside the expertise of the patent holder. Alternatively, you may be able to develop a formal collaboration with the patent holder to explore the drug for a new use or population.

8.1 Drug Repurposing

Expanding indications of use for an FDA-approved drug may be related to the initial indication/disease family or may be unrelated to the initial indication. Drug repurposing (drug repositioning, reprofiling, or re-tasking) identifies new uses of an approved or investigational drug. Drug repurposing may use compounds shown to be safe for human use in mid or late-stage clinical trials where development was stopped due to lack of efficacy in a clinical trial.

Drug repurposing allows you to use or reference previously conducted preclinical and clinical investigations in your IND application, decreasing the cost of bringing the drug into the new population.

One example of this is remdesivir—an antiviral therapy developed initially as a therapy for hepatitis C—which was later repurposed for treatment of Ebola and the Marburg virus. It also received **Emergency Use Authorization** for the treatment of SARS-CoV2.

There are two regulatory pathways to request market approval for drug repurposing: NDA and Abbreviated NDA.

Resources:
NIH: NCATS Drug Repurposing Program

8.2 Bringing a Foreign Drug to Market in the U.S.

The U.S. healthcare system is an attractive market for drug developers. If a drug is not available in the U.S. but is legally marketed in another country, you may be able to use data collected from the international use/approval of the drug. Many countries manage and review drug development data using guidelines developed by the International Council for Harmonization—a consortium of pharmaceutical companies and regulators that have developed and adopted unified expectations for drug and biologic product development.

When bringing a non-U.S. drug into the U.S. market, ensure you have rights to current intellectual property or plan to develop new intellectual property relevant to the drug. You should also meet with FDA to determine if there are limitations on using data collected outside the U.S.

Resources:
FDA: FDA Acceptance of Foreign Clinical Studies Not Conducted Under an IND FAQs
FDA: E5 Ethnic Factors in the Acceptability of Foreign Clinical Data

Appendix A Guidance for Selecting a CMO and Outsourcing

For many academic innovators, start-ups, and mid-size companies, choosing a Contract Manufacturing Organization (CMO) for their lead product candidate is critical for manufacturing the product under cGMP (current Good Manufacturing Practices) compliant and controlled processes. Therefore, before initiation of outsourcing activities and signing of the contract, the innovator should conduct due diligence to identify and choose the right manufacturing partner based on (a) product(s) needs and (b) the basis that the CMO is a good fit for the product development lifecycle. As part of this process, the innovator will have to solicit a proposal to seek CMO information before the CMO selection process.

This preliminary process usually involves the following steps.

Step 1: Circulate the Request for Proposal (RFP) to multiple CMO bidders (3-5) to optimize CMO selection.

Be very clear about the services requested from the CMO to be quoted. For example, depending on data in hand and maturity of the development process/platform, project the scale, number of batches, process development, engineering batches (if required), quality assurance, and regulatory support. In addition, be clear about the expectations from project management and the expected number of meetings and on-site visits. This can be very helpful for the CMO and the Innovator to compare quotes once received.

Step 2: In writing, define the scope, including working assumptions and expectations.

List everything critical for the product (even if not demonstrated), including the process, product, yield, release assays, product stability, regulatory filings and outcomes, and future events that cannot be known at the time of the proposal. Also, define if the material (API, cell-substrate, reference standard, etc.), process, and product analytics will be tech transferred.

Step 3: In response to the RFP, review the CMO responses to the various line items, deliverables, milestones, and budget and if they address the above requirements for the phase-appropriate product development.

Step 4: Contractually ensure that the scope of services for proposal and quotation support the required and supporting activities as defined in the RFP.

Selecting a CMO, and crafting a contract with it, is one of the most critical and complex business decisions for a company. You will be sharing the intellectual property with the CMO, creating significant intellectual property as it scales up the product and continues its development. You can also consider bringing on board an experienced expert who can guide you through the vendor selection and contracting process, who knows what to look for, what to look out for, and how to avoid typical pitfalls. Ultimately, you will have to assess the decisions and merits of the CMO based on a case-by-case basis, considering its internal pipeline and strategy, budget/funding, and risks.

Resource:
NIH SEED: An Innovator's Quick Start Guide to CMOs and CDMOs
NIH SEED: Innovator Checklist for Finding a Contract Manufacturing Organization

Updated November 2023