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GUIDE

505(b)(2) CMC Basics: Aligning Chemistry, Manufacturing, and Controls with Clinical Trial Phases

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All pharmaceutical companies share a common goal, regardless of their size or history: for their products to achieve commercial status and success through the most time- and cost-efficient development path. The 505(b)(2) regulatory pathway was established to offer efficiency benefits for clinical, nonclinical, and chemistry, manufacturing, and controls (CMC) product development. Often sponsors, particularly start-ups and mid-size companies, concentrate their limited resources, expertise, and funding on clinical development, while deprioritizing the CMC development strategy. While the successful completion of clinical trials can certainly help to invite and maintain funding, those trials are not meaningful without an appropriately designed, manufactured, and controlled drug product.

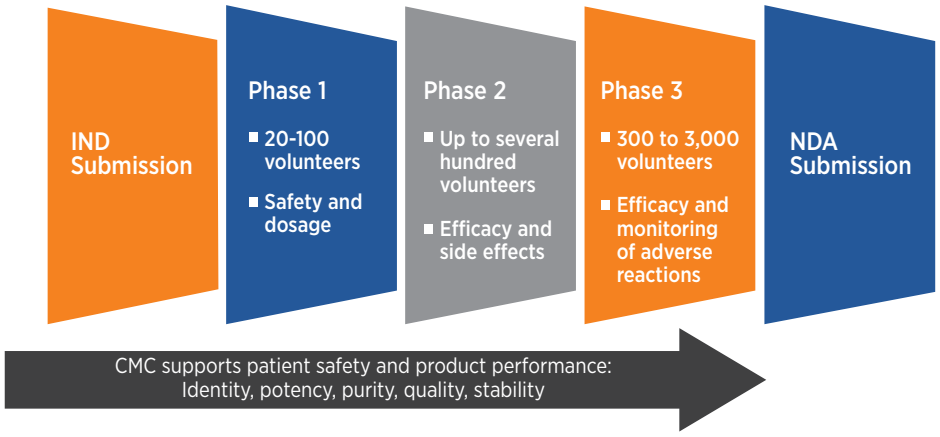


Figure 1. Drug development and clinical trials: Phases 1, 2, and 3

Since the purpose of clinical trials is to assess the drug product's safety and efficacy, product development plans must account for the identity, potency, purity, quality, and stability requirements expected by the FDA, patients, and medical care providers (Figure 1). If the CMC information is not correctly scaled at each phase of development, this may lead to clinical holds, which in turn may result in project timeline delays. Therefore, it is essential that CMC development be at the appropriate stage to support dosing in clinical trials.

Importantly, a clinical drug product should be representative of the commercial drug product. Otherwise, appropriate bridging is required between the product used in clinical trials and the proposed commercial drug product. Depending on the type of changes, this bridging may require additional *in vitro* and *in vivo* data.

Phase-appropriate CMC documentation

A successful program requires a that **quality target product profile (QTPP)** be established as early as possible during development. The QTPP describes the design criteria for the product under development and is the foundation for both defining critical quality attributes and critical process parameters and establishing a control strategy for the proposed product and associated manufacturing process.

Product development is a lengthy process, and product history and knowledge are built through data collection over time; therefore, modifications to the method of preparation of a new drug substance and drug product are likely. In acknowledgement of this reality, the FDA has published guidelines to summarize the required CMC information at various phases of development, including:

- Code of Federal Regulations Title 21 CFR 312.23 (a)(7)
- Guidance for Industry: Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs, Including Well-Characterized, Therapeutic, Biotechnology-derived Products
- Guidance for Industry: IND Applications for Clinical Investigations: CMC Information
- Guidance for Industry: INDs for Phase 2 and Phase 3 Studies: CMC Information

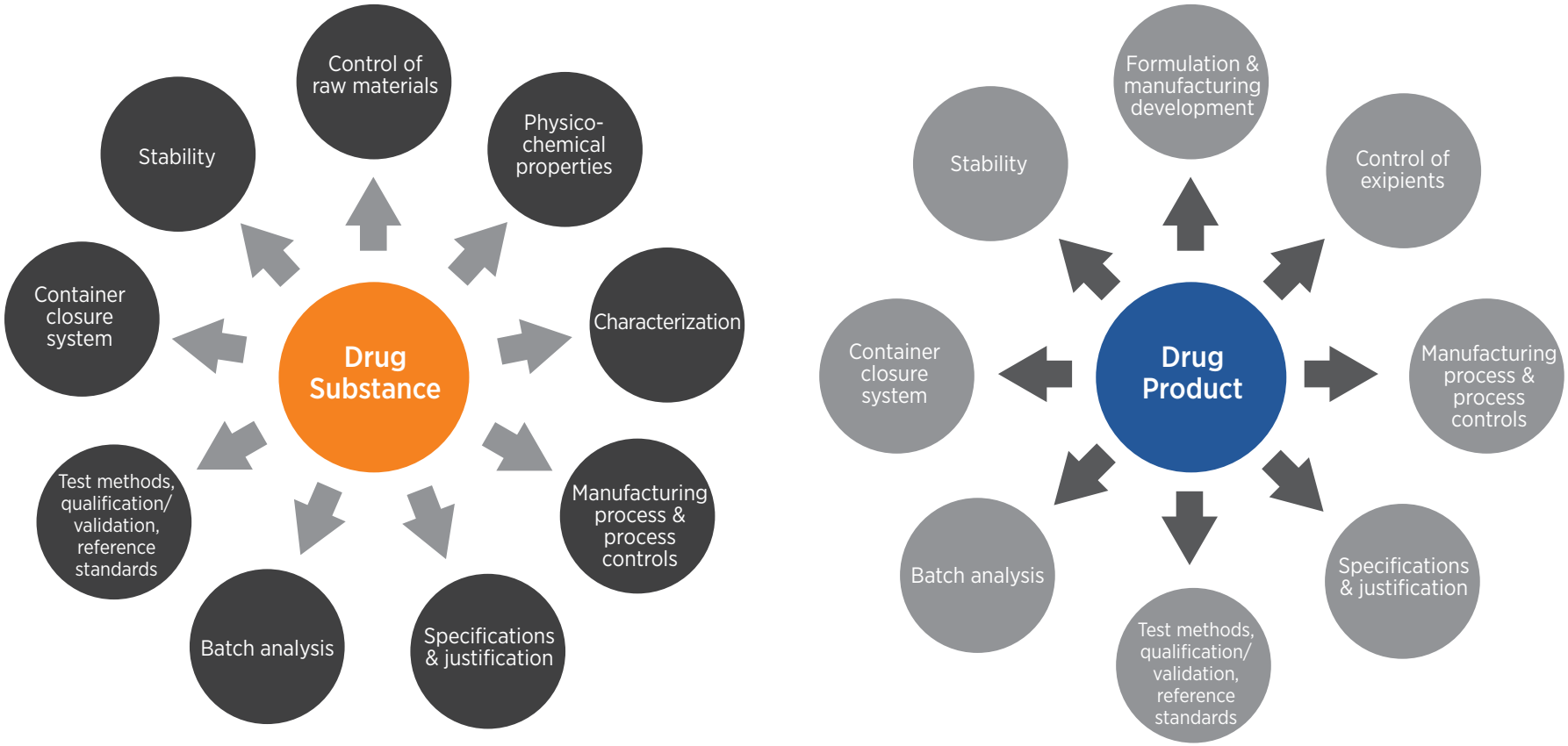
The FDA's guidance documents provide general instructions about the required CMC information with the highest emphasis placed on human safety:

Although in each phase of the investigation sufficient information is required to be submitted to assure the proper identification, quality, purity, and strength of the investigational drug, the amount of information needed to make that assurance will vary with the phase of the investigation, the proposed duration of the investigation, the dosage form, and the amount of information otherwise available.[1]

... [T]he CMC component is expected to address whether any information regarding the chemistry and composition of the drug substance, drug product, or the manufacture of either might suggest any possible human risks.[2]

A schematic of CMC information required during development is shown in Figure 2.

Figure 2. CMC required information during development



CMC requirements for Phase 1: Key considerations

There are several key factors involved in planning Phase 1 clinical trials from a CMC perspective:

- Phase 1 CMC information must support human safety and demonstrate through data that the product intended for clinical trials meets early development specifications for drug substances, drug/combination products, and excipients.
- Sponsors must generate stability data in the container closure system to be used during the clinical trials to demonstrate that the product remains stable and safe throughout the duration of the clinical trials.
- Test methods must be qualified or validated, as applicable, according to the stage of development.

CMC requirements for Phase 2 and Phase 3: Key considerations

For Phase 2 and Phase 3, implemented controls are expected to increase and be more vigorous based on accumulated development data.

- Specifications may be tightened based on increased product knowledge.
- Transfer and scale-up activities are possible and must be described.
- Since Phase 3 studies generally provide most of the safety and efficacy information to support an NDA submission, **it is strongly recommended that Phase 3 studies be performed with product representative of the to-be-marketed product** in terms of formulation, manufacturing process, and container closure system.
- As in Phase 1, test methods must be qualified or validated, as applicable.

Challenges of CMC strategy when supporting clinical trials in 505(b)(2)

FDA guidances make it clear that, as development progresses through its various phases, patient safety remains critical, while the CMC information available must progressively increase. However, many sponsors remain unsure about what CMC information needs to be filed at which development phase. One example is the use of phase-appropriate analytical methods and their qualification or validation status. Furthermore, depending on the route of administration, sterility requirements, or novelty of the drug product, additional product-specific considerations may apply. In other words, **a "one-size-fits-all" approach is not applicable in the CMC development and strategy.**

A product-tailored CMC approach is not limited to specific scientific considerations, such as comparing an oral tablet formulation to a prefilled syringe combination product – it also applies to the overall regulatory strategy timelines. In the case of the 505(b)(2) regulatory pathway, a sponsor may be able to abbreviate the nonclinical and clinical program by using already-available regulatory information. In such cases, the CMC program may become rate-limiting at the time of regulatory filings. (Similarly, accelerated programs such as fast track or breakthrough therapy designation require rapid CMC development in order for a sponsor to reap their full benefits.)

While a sponsor may have identified a promising formulation, stability data collection is a time-consuming process that must be accounted for as early as possible. And, contrary to a popular misconception, when following the 505(b)(2) regulatory pathway, stability data may need to be collected not only for the drug product but also for the drug substance, including for a novel drug substance such as a prodrug, a deuterated molecule, or an isolated enantiomer of an existing moiety.

Across every phase of product development, CMC experience is essential in achieving a product that meets regulatory standards and avoiding unnecessary development costs and timeline delays. Premier Consulting has deep technical and regulatory CMC expertise and has successfully supported multiple projects at all stages of development. Contact us today to find out how we can support your program.

References

1. U. S. Food and Drug Administration. CFR - Code of Federal Regulations Title 21. Available at https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?fr=312.23.

2. U. S. Food and Drug Administration. IND Applications for Clinical Investigations: Chemistry, Manufacturing, and Control (CMC) Information. Available at https://www.fda.gov/drugs/investigational-new-drug-ind-application/ind-applications-clinical-investigations-chemistry-manufacturing-and-control-cmc-information.

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