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WHITE PAPER

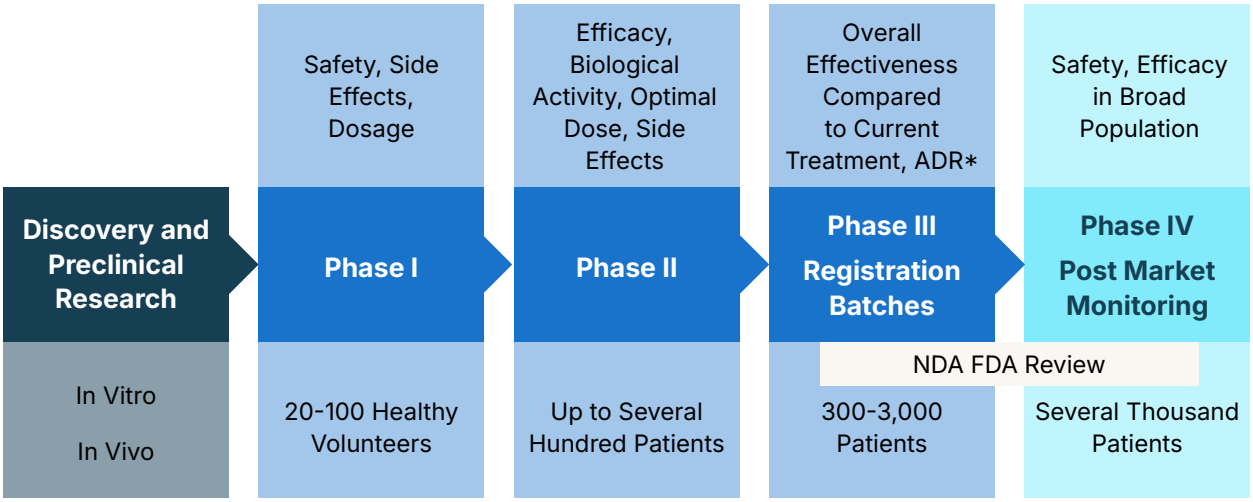
Phase Appropriate CMC Considerations for Oral Solid Dosage Forms of Small Molecules (US Market)

Drug Development Process

A typical drug product development process involves five steps: Discovery and Development, Preclinical Research, Clinical Research, FDA Review, and Post-Market Safety Monitoring.

Testing in human subjects begins in the clinical research phase, which is further divided into four phases (Phase 1 to Phase 4), each with a different study objective and subject requirements, and therefore also with the different CMC (Chemistry, Manufacturing, and Controls) requirements.

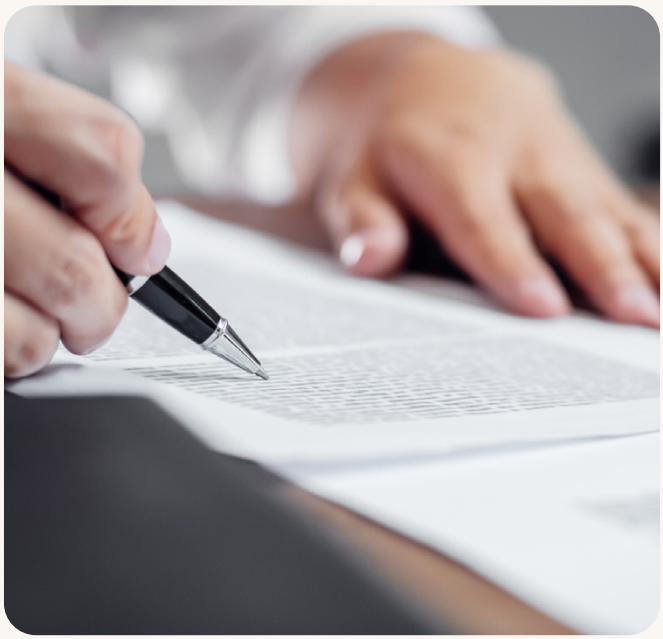
Figure 1: Drug Development Process



*ADR: Adverse Drug Reaction

An overview of the general CMC considerations based on common industry-adopted drug development approaches for various phases of oral solid drug product development of small molecules for the US market is presented in the following sections.

GLP/cGMP Considerations



According to the 'FDA Guidance for Industry: cGMP for Phase 1 Investigational Drugs', Phase 1 investigational drugs are excluded from complying with the cGMP regulations in 21 CFR part 211. The guidance recommends appropriate controls during development, and compliance with statutory cGMP regulation under 501(a)(2)(B) of the 'FD&C Act' during the manufacture of clinical batches while following sound scientific and QC principles to ensure the safety and quality of Phase 1 investigational drugs. The guidance is not applicable to drugs that have already been manufactured for use in Phase 2 or Phase 3 trials or have already been marketed. In such cases, compliance with cGMP regulations is required.

Drug Substance

In Phase 1, a brief description of the drug substance, its manufacturing process, and some evidence to support its proposed chemical structure should be established. In Phase 2, a more detailed description of the configuration and chemical structure for complex organic compounds, general description and a flow diagram of the synthesis/ manufacturing process should be available. In addition, data on the particle size distribution and other physical properties (e.g., polymorph or solid-state form) should be generated as feasible. New impurities (e.g., from a change in the synthetic pathway) should be identified, qualified, quantified, and reported as appropriate.

In Phase 3, structure elucidation and characterization, including elemental analysis, conformational analysis, molecular weight determination, etc., should be conducted. Physical, chemical, and biological characterization of the drug substance, e.g., solubility, pKa, hygroscopicity, crystal properties and morphology, thermal analysis, optical rotation, biological activities, etc., should be performed. In addition, a general step-by-step description of the synthesis/ manufacturing processes, including batch size (range), process controls, general operating conditions, control of critical steps and intermediates, reprocessing procedures and appropriate controls, etc., should be available. Suitable microbial limits should be established for non-sterile products with microbial growth potential.

Excipients

Several factors, such as excipient function, compatibility with the drug substance and other formulation components, excipient quality, compendial status, etc. govern the excipient selection from early-to-late-stage development.

Table 1: Phase-appropriate Considerations for Excipient Quality Control

Phase I	Phase II	Phase III
Minimum excipient control that includes appropriate labeling, segregation, and storage to prevent degradation or contamination should be established. Materials should be identifiable and traceable. Acceptance criteria should be established for the key material attributes and can be confirmed from the vendor certificate of analysis. All relevant attributes and acceptance criteria for all materials may not be available in Phase 1.	Excipient quality shall be assessed per the compendial standards. For non-compendial excipients, specifications shall be developed that identifies key tests, test methods, and acceptance criteria. A brief description of the manufacture and control of these components or an appropriate reference should be provided (e.g., DMF, NDA) in IND submission.	Additional tests beyond compendial standards shall be considered, as appropriate, to ensure the quality of key functional excipients. For non-compendial excipients, a full description of the characterization, manufacture, control, analytical procedures, and acceptance criteria should be provided in the IND submission.

Novel excipients shall be evaluated with an approach similar to that of the drug substance.

Batch Size

Clinical batch size for different phases depends on the formulation approach, API availability, clinical study design (number of subjects and dosing duration), analytical testing requirement, stability study design, retention samples, manufacturing equipment capacity, process losses, etc. The number of subjects, formulation and process development, and testing requirements often increase along the development phases. Thus, the batch size generally increases as the drug development phases progress. The batch size for registration batches in Phase 3 development should be 1/10th of the commercial batch size or 100,000 units/batch, whichever is greater.

Formulation Development

Dosage form selection is governed by the physicochemical and pharmacological properties of the drug substance that are evaluated during preclinical research and pre-formulation studies. For example, for drugs with adequate bioavailability and suitable physicochemical characteristics, the minimal approach could be using a simple API in capsule, API solution, or API suspension in a phase 1 clinical study. Many drug developers prefer delaying extensive formulation development studies until the later phases of development. This enables quick access to the clinic with reduced API consumption. However, it's advantageous to evaluate the impact of excipients, dosage form, etc., on in-vivo product performance during the early stages. The choices made early in the formulation development can impact the later-stage development. In some instances, depending on the drug substance properties, formulation screening might be necessary from the early phase of development, e.g., developing a more bioavailable formulation using technologies such as spray-dried dispersions, hot melt extrusion, etc. at Phase 1 for drugs with low aqueous solubility, or poor systemic absorption. Formulation development advances with each successive phase of development. By Phase 3, the formulation should have been optimized to achieve the best product quality, stability, clinical outcome, and patient acceptability. The impact of critical material attributes should be evaluated on drug product critical quality attributes (CQAs), and a control strategy should be developed for them. A design space for key CQAs should also be defined that allows for reproducible product quality to be achieved with minor manufacturing changes.

Manufacturing Process

In the early stages of development, often, the batch size is small, and the manufacturing process is not well established. Knowledge about the investigational drug is limited, and comprehensive characterization techniques might not be available. Well-documented processes with simple process controls based on a preliminary risk assessment at initial phases are sufficient. For small batches, manual or semiautomatic processes could be a quick and cost-saving approach, especially when the resources are limited.

Manufacturing processes, process parameters, and controls are more defined during Phase 2/3. Process optimization and scale-up studies are often performed at this stage. Key factors to consider while developing a robust manufacturing process include operating principles of equipment, equipment capacity, operating ranges for process variables, in-process quality monitoring, etc. Critical process parameters shall be evaluated, and a control strategy for them should be developed by the time registration batches are manufactured. Quality by Design (QbD) and DoE (Design of Experiment) based development with more advanced process monitoring, such as using Process Analytical Technology (PAT), is encouraged at this stage. Process validation for commercial manufacturing processes is not required at the pre-NDA stage but can be initiated if desired.

If the dosage form, formulation composition, or manufacturing process are changed at any phases of clinical development and the change affects product equivalency as determined by analytical testing, sponsors should perform additional qualification and/or bridging studies to support safety and bioavailability of the material to be used in the proposed trials and, when applicable, to support the quality of the trials.

Analytical Methods

Analytical tests are used to evaluate materials – drug substance, excipients, packaging components, in-process material, finished drug product, stability samples, etc. to ensure product quality with respect to identity, strength, potency, and purity, as appropriate. In the early phases, formulations and processes are not fully established, and analytical knowledge is limited. For example, process scale-up during late stages may generate a new impurity profile which might not have been observed during early small-scale development. Thus, analytical development also progresses along with the phases of development.

In Phase 1, simple test methods e.g., IR spectrum to prove the identity and HPLC chromatograms to support the purity level and impurities profile of the drug substance should be established which are often adopted for the drug product analysis. The development of stability-indicating analytical test methods should be considered in Phase 2. At early stages, compendial methods should be verified, and non-compendial methods should be suitably qualified for the analysis. According to the FDA Guidance for Industry on 'Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs Including Well-Characterized, Therapeutic, Biotechnology-derived Products', validation data and established specifications ordinarily need not be submitted at the initial stage of drug development. However, specifications should be developed with the current product understanding to ensure product safety and efficacy. Acceptance criteria should be specified for critical attributes such as potency, purity, etc. The acceptance criteria listed as 'Report Results' for other tests are acceptable until sufficient information is collected. Specifications for Phase 3 investigational drugs should be more in line with the anticipated final commercial specifications. As the formulation and manufacturing process become more established, risk assessments for elemental impurities, residual solvents, and nitrosamines are usually performed before manufacturing registration batches. Based on the risk assessment, a control strategy for these attributes should be defined, considering the potential sources of these impurities such as raw materials, manufacturing equipment, and the container-closure system. Test methods should be validated as per ICH guidelines before the stability testing of the registration batches is initiated. Once the methods are validated, if the GMP testing facility is different from the method validation facility, appropriate method transfer, and re-validation criteria should be applied before the testing.

Table 2: Phase-appropriate Method Performance/Validation – General Recommendations

	Phase I	Phase II	Phase III
Raw Materials	Use test, Specificity	Use test, Specificity, Accuracy, Linearity	Phase 2 activities + Robustness
Drug Product	Specificity, Linearity Accuracy + Precision, LOD/LOQ	Phase 1 activities + Intermediate precision	Full ICH (Phase 2 activities + Reproducibility + Robustness + Specificity with forced degradation)

Reference: Sue Schniepp et al. GMPs for Early-Stage Development Projects. Regulatory Compliance Associates.

Stability

During Phase 1, initiation of a stability study to monitor stability and quality of the Phase 1 investigational drug during the clinical trial (i.e., date of manufacture through date of last administration) is recommended though detailed stability data or protocol are not needed for IND submission at this stage.

In Phase 2, a description of the stability performance for the submission should include a list of the tests, analytical procedures, acceptance criteria, time point for each test, storage conditions, and duration of the study which should be long enough to cover the expected duration of the clinical trials. Development of stability-indicating analytical procedures and conducting stress studies should be considered at this stage.

In Phase 3, long-term and accelerated stability studies should be carried out on the drug substance and the drug product in a container closure system that simulates the container closure system used to transport and/or store the material. Stress studies, if not carried out earlier, should be conducted during Phase 3. Phase 3 stability studies are often used as the registration stability study, but they can be separate studies. Stability protocol as per ICH guidelines for stability studies and a minimum of 12M long-term stability data on 3 batches are needed for NDA filing.

After approval, sponsors are required to undertake stability studies on at least one lot per strength and per packaging configuration under long-term conditions each year as the product is manufactured.

Conclusion

The drug development process is divided into multiple phases. The CMC considerations vary with the phases of clinical research. A drug developer can take different approaches to accomplish the drug development goal, meeting the essential requirements of each clinical research phase. An overview of the phase-appropriate CMC considerations was provided in this paper based on the common industry-adopted drug development approaches for oral solid drug products of small molecules for the US market.

REFERENCES

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