



PROCESS AND FORMULATION DEVELOPMENT CONSIDERATIONS

Expedited clinical development programs for breakthrough therapy products will shorten the time available to optimize phase III and commercial manufacturing processes. This will necessitate prioritization of development efforts on process reliability over yield and cost of goods. As a result, process and formulation optimization may need to be deferred to post-approval; if it can be determined, there is no impact on patient safety or product availability.

Some activities that might be considered to speed development activities include the following:

- Launching commercial processes with limited experience, but sufficient data to ensure that the process can reliably produce a drug to meet the expected quality safety and efficacy profile and optimize post-approval
- Using data from development material or the clinical supplies, with adequate comparability data to supporting material from initial commercial process lots, may be needed
- Consider delaying intermediate hold time studies and instead do straight-through processing and scheduling of intermediates to speed process development
- Lock the phase I/II drug product formulation and optimize post-approval to avoid the need for bioequivalence studies
- If efficacy is indicated in phase I clinical studies, in oncology patients, sponsors may want to strive for a commercial dosage form to be used in the pivotal phase II clinical program
- For biologic products, optimize cell line development early and carry through phase III and commercial production
- For small-molecule products, the focus should be on the active pharmaceutical ingredient (API) and excipient attributes impacting formulation and DP manufacturability and performance
- Consider close alignment on linkages in control strategies (e.g., particle size distribution impact on dissolution for small molecule drugs) and overarching themes that might apply to both biologics and small molecule drugs (e.g., moisture-sensitive API)

Formulation and Manufacturing Process (small molecule)

Over the last 10 years, there has been considerable development in computer simulation of pharmaceutical materials, processes, and product performance. Increasingly, mechanistically based models provide a sound basis for describing 'prior knowledge of the behavior of the systems being described. The increase in available models provides an unprecedented opportunity to apply a systems-based approach to formulation and process design linked to pharmaceutical product quality and performance.

Specifically, in an expedited development paradigm, in-silico tools can be utilized for formulation and process selection with the associated mechanistic understanding of in-vitro and in-vivo performance, including the impact of product stability. In many cases, these models can be built or calibrated using specific experimental measurements of physical properties or one to a few carefully designed experiments, rather than relying on a purely empirical understanding driven by extensive experimental design methodologies.

It is important to recognize that the prior knowledge that comes with the utilization of models allows greater product and process understanding to be obtained from experimental calibration and validation, rather than experimental mapping or interpolation. This will also lead to enhanced process establishment with reduced experimental packages, speeding up clinical supply and ultimately commercial supply. Furthermore, the impact of unseen future changes (for example, raw materials) can be anticipated and explored using models, thereby improving future process capability and security of supply for patients.



Continuous Manufacturing (small molecules and large molecules)

Traditional batch processes for the manufacture of both drug substance and drug product are being complemented using continuous processing methods. The use of continuous processes allows innovative methods of drug substance manufacture to be used (for example, the use of highly selective reactions or otherwise hazardous materials). Due to the nature of the equipment, it is possible to rapidly develop the manufacturing process, for example, to optimize reaction conditions and to assess critical manufacturing parameters.

Once developed, the scale-up of continuous processes is, to some extent, easier to predict than for batch processes therefore the quality of material produced at laboratory scale is likely to be indicative of the quality produced at commercial scale manufacture. It also offers benefits for the supply chain for products where the predicted volumes of drug substance and drug product are uncertain i.e. it is easier to stop and start continuous processes than batch processes. This methodology is also amenable to innovative analytical methods such as in-line process monitoring which can be used for continuous process verification.

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