DS INPHARMATICS
A ProductLife Group Company

MANAGING PHASE 2 CMC RISK

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About The Author

Head of CMC Drug Development and consulting services practice. Tony has 30 years of senior management experience in drug development, cGMP manufacturing, and commercialization; including hands-on plant management, budgeting, and strategic planning. His experience spans a broad range of small molecule and biologic dosage forms and all aspects of technical and manufacturing operations from active pharmaceutical ingredient (API) through fill and finishing operations for clinical and commercial launch; including Synercid®, Abelcet®, Myocet®, Taxotere®, Nasacort®, Lovenox®, Thymitaq®, lixivaptan, and rM-CSF.

Small pharmaceutical companies with early-stage drug development programs operate under pressure from investors to demonstrate proof in man results quickly. In this context, investors seek to maximize return on investment by reducing both the cost of development and the time to market.

Managers of development companies typically find themselves advancing a drug product to the next valuation milestone with limited resources in a relatively short period of time.

Big pharma companies typically spend more time and resources on pre-clinical animal modeling and undertake formulation development using a systemic approach to optimize drug formulation based upon extensive chemical and physical characterization of the active drug molecules and interaction with a range of excipients. The resulting drug product enters pre-clinical development with a PK/PD profile optimized to meet a specified dosage and delivery profile.

In contrast, small development companies advance a drug candidate based on little more than a scientific rationale target(s) and some promising nonclinical biological activity. Facing financial and time pressures, they typically elect to test a set of standard excipient combinations in accelerated stability studies with the hopes of quickly finding a formulation that will be ‘good enough' for the early stages of development. For example, small molecules are frequently formulated as immediate-release tablets or capsules with granulation or as a “neat” active pharmaceutical ingredient powder fill (API) with a few or no excipients.

Since a drug product's dosing and delivery profile is in most cases a primary determinant in its ultimate marketability, commercial success, and valuation prospects, it is important to balance clinical expedience with a long-term strategy that provides a regulatory pathway for later formulation and manufacturing process changes.

Formulation Regulatory Strategies

1. Start with a less complicated or less marketable formulation to just get approval and save the more complicated formulation for a post-approval change line extension.
2. Conduct early clinical trials with the less complicated formulation/dosage form and then a bioequivalency study to bridge to Phase 3.
3. Under certain conditions, it may even be possible to piggyback on earlier supporting data of a formulation, perhaps filed in an IND or already marketed product.

Each step along the path from discovery to commercialization is important, and an effective chemistry, manufacturing, and controls (CMC) process plays an integral role in the success of a compound.

About DS Inpharmatics

DSI is a full-service CMC Drug Development and Regulatory Affairs consulting firm combining in-depth technical knowledge of product development with regulatory strategy and content authoring for all phases of the review and approval process in the U.S., Canada, and Europe.

Our group practice is composed of pharmaceutical scientists with decades of drug development experience in each subdiscipline of Chemistry, Manufacturing, and Controls. Whether your needs are comprehensive or tightly focused, DSI will help you keep your drug development program on track and under budget.

Not just advice. DSI provides you with flexible scientific resources to fill in-house expertise gaps and expanded operational capability to design and implement compliant drug development programs.

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CMC requirements are minimal for filing Phase 1 IND. The active pharmaceutical ingredient (API) must be adequately characterized to provide support of its proposed molecular structure, MW, crystal structure, and form (i.e. salt, hydrate, solvate). Stability data on a representative lot is required to support to the expected duration of the clinical trial; however, a fully ICH compliant protocol is not necessary at this stage.

If you have limited resources during Phase 1, CMC expenditures should focus on the development of stability-indicating analytical methods. The ability to assure, over time, the physical and chemical properties of an active pharmaceutical ingredient or drug product is critical for regulatory approval.

Stability indicating assays provide important supporting data linking changes made to later clinical trial materials back to early pre-clinical work (i.e. toxicology). That is to say that the analytical methods should allow for comparisons of API and Drug Product used in earlier work as well as future trials.

Accelerated stability studies are useful to identify potential degradation pathways, impurities, and chemical modifications that can affect the structure and composition of the drum product. Using degraded samples during method development can ensure that all peaks show up initially. The key here is to develop sensitivity when your analytical methods are capable of separating non-active ingredient peaks from the API. For forced degradation studies (e.g., temperature, humidity, and light) can follow the leader. The hope is that conditions for forced degradation studies do not result in any new, on identified peaks that may require additional toxicology studies. It's stressed degraded samples are used; then the risk is usually fairly minimal.

CMC changes that can affect safety are

- Change in synthetic pathway/impurity profile
- Change in material source
- Method of sterilization
- Composition of drug product

The question of impurities has become a major focus of both the FDA and EMEA. A detailed review of a product impurity profile can be expected when a Phase 3 IND and IMPD are submitted.

Beginning studies in phase 2 to identify critical manufacturing steps, process parameters, and control specifications provide basic process knowledge that can allow drug manufacturers time to troubleshoot and develop alternative strategies for dealing with these issues prior to entering pivotal Phase 3 trials.

Once Phase 3 trials are initiated, it becomes presumably more difficult to make product formulation and process changes to address problems with degradants and impurities; since they can trigger regulatory requirements for additional toxicity or bioequivalence trials.

Here is where there early investment and analytical methods can pay big dividends by helping companies avoid protracted delays due to questions regarding the qualification Of impurities. The accurate and linear methodology can detect and resolve low levels of impurities and will allow a sponsor to develop trending data. This can allow for comparisons of pre-clinical toxicology data with current clinical material Data and allows for the extrapolation of effects at new levels. Lastly, process changes can be reviewed in light of the effects that they have on product impurity profiles.

How many drug development programs fail or are significantly compromised due to product stability issues. For example, the shelf life of clinical trial materials can become a crisis when a clinical trial has a slower recruitment rate than predicted or is extended due to positive results. Early investments in characterizing degradation and denaturation pathways provide a strong knowledge base for troubleshooting stability problems and selecting alternate excipients or synthetic processes that slow or avoid these problems.

It is important not to hold all CMC expenses until after Phase 2; because the simplistic investment approach can increase the actual risk of clinical holds or delays. A more rational approach is the focus investment in areas where supporting data can be developed to address key safety concerns.