DSINPHARMATICS
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TOP FIVE CMC CLINICAL HOLDS

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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.

Sometimes the drug development process is stalled by matters of efficacy, but just as often delays are the result of common and avoidable errors in the realm of Chemical, Manufacturing & Controls (CMC). Here we take a look at five of the most common of these errors and offer ideas on how you can prevent them from slowing your approval process.

1. Failure to meet regulatory requirements in IND/IMPD filings
While the regulatory expectations for a Phase 1 Investigational Drug (an IND in the United States or an IMPD in the European Union) are not as demanding as they become later in the process, you will be required to demonstrate support for adequate patient safety as well as to establish a baseline for evaluating changes in the drug over the course of the clinical studies. Specifically, you should be prepared to provide the following: a reliable material characterization; a methodology for testing release and stability; specifications that allow control of identity, strength, and purity; evidence of stability over the life of Phase 1 clinical trial; evidence of the ability produce the described product on a commercial scale. Collecting and accurately reporting these data will go a long way toward advancing the progress of your Drug Product through later development stages.

2. Chemical and Physical Stability
By Phase 2 and Phase 3, you're expected to have far better data regarding the chemical and physical stability of your Drug Product and API. Once you begin to manufacture larger batches in which the formulations and dosage forms mirror those of your commercial product, your product stability will be expected to meet current International Conference on Harmonization (ICH) guidelines (Q1A-Q1F). You'll also need to demonstrate shelf life sufficient to ensure safety throughout the entire course of a clinical trial. Data trend analysis and ongoing method optimization combined with ICH compliant stability programs can help detect and correct problems early on that could otherwise lead to more serious clinical delays.

3. Product Contamination and Impurities
Clinical Trial Materials (CTM) bearing contaminants or impurities are regarded as "adulterated" and must undergo a costly and time-consuming process to determine the cause (most typically lack of sterility, careless handling of raw materials or cross-contamination from other products and processes). A strong, independent Quality Unit and rigorous audits of manufacturing facilities are essential. The alternative is diagnosing the cause of the problem, correcting it and running new, clean batches which can put your entire program way behind and over-budget. In addition, regulatory agencies in the U.S. and Europe have begun paying much more attention to impurity profiles, making it imperative to develop methods that are accurate and precise enough to detect even the lowest levels of impurities.

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.

4. Material Characterization
To accurately assess possible safety and stability issues, reviewers need sponsors to provide thorough and precise Material Characterizations. Without them, you can expect a barrage of questions about your API and Drug Product at EOP2 meetings and IMPD updates. Salt forms, polymorphs, crystalline structure determinations, and definition of the "regulatory starting materials" should be included in molecular characterizations. For biologic APIs, you must provide an adequate history to strain and construct development, identity, and purity of source materials, including viral and adventitious agent testing. Finally, API and Drug Product must be shown to be free of bovine spongiform encephalopathy and transmissible spongiform encephalopathies (BSE/TSE). Early attention to meeting these requirements, will help pave the way toward commercial approval.

5. Mislabeling
While, in theory, mislabeling should be easy to avoid, and thus very rare, it actually occurs far more often than you might expect. One reason for these problems is the increasing trend toward giving the responsibility for manufacturing, labeling, and distributing clinical trial materials to Contract Manufacturing Organizations (CMO). Errors ranging from the omission of key information or erroneous Med-ID numbers in blind trials to foreign-language translation mistakes are becoming increasingly common. This ongoing problem points to the importance of carefully assessing the compliance record and competence of your chosen CMO, and then following up with a stringent audit.

Plan ahead and follow-up to prevent CMC-driven delays
Insufficient planning often leads to CMC errors and oversize they can result in serious, highly visible delays getting promising drugs to market. These delays are not only costly to the sponsor, but to patients who could benefit from the drug, as well. Proactive steps such as vendor audits, independent QA reviews, thorough filings, and preparation for review meetings can all help prevent problems. Because human beings are an integral part of every process, it may be impossible to entirely illuminate every error. But knowing where to focus your attention can often be enough to head off trouble before it has a chance to develop into a costly and time-consuming delay.

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