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Embracing A New Standard For Regulatory Development: 3 Key Considerations For Phase-Appropriate GMPs

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Navigating product development is inherently difficult. Ambiguous global regulations and complex submission requirements make questions and challenges inevitable. Because regulatory requirements and GMP expectations increase as product development proceeds, many biopharmaceutical manufacturers wait until late stages to make Good Manufacturing Practices (GMP) a priority.

By integrating GMP this way, manufacturers attempt to increase speed to market and reduce overhead. However, waiting to implement GMP frequently leads to significant operational challenges, as both the FDA and EU give the ability to be flexible during Phase I, increasing requirement stringency for Phase II and Phase III processes. Accordingly, as manufacturers move their product from research to clinical phases, these requirements often become a bottleneck, potentially impacting commercial timelines and inflating budgets. Further, it has become increasingly difficult to maintain a uniform interpretation of regulatory norms in recent years, at both the corporate and industry levels.

By taking a strategic, proactive approach to regulatory and process development, you better position your organization to avoid unexpected challenges. Here, we will provide three key steps you can take to implement a regulatory framework to the highest standards.

1. PROJECT TIMELINES

Ideally, you want your process development to arrive at Phase III's strict standards with minimal friction. Fortunately, time to clinical development – and ultimately, to market – is a marathon, not a sprint. You have time to look ahead, anticipate challenges, and implement solutions early on. As commercial timelines grow increasingly aggressive, it is important to remember that now, more than ever, due diligence is both essential and beneficial.

For instance, you may be inclined to test using non-GMP grade materials during research or toxicology phases. However, knowing that safety and efficacy trials will require GMP adherence, it is advisable to use GMP materials early on. Although GMP materials result higher costs, they provide real value from a risk mitigation perspective by helping you avoid formulary complications during tech transfer. This is especially relevant if you are working with complex or highly reactive raw materials.

Holding a long view may be increasingly important as we step into a new and uncertain future. At the time of this article's publication, the world is battling a grave pandemic: COVID-19. The urgent need for treatments and a vaccine has industry racing to develop products, with unprecedented project timelines. These timelines may alter the way manufacturers look at regulatory timelines going forward, and as the global economy moves towards recovery, speed may be emphasized over due diligence. However, to avoid disruptive challenges, discipline and a measured approach should prevail.

2. EARLY STAGE STRATEGY

Ideally, in addition to formula development, your pre-development and research phases should

be used to anticipate and meet important regulatory requirements. From a regulatory standpoint, you are expected to provide a detailed rationale of every major decision regarding process development, including R/D.

It is common knowledge that the most important document regulatory agencies will assess is your technology transfer plan. However, in situations where contingencies and risk analysis fall short (in the eyes of regulatory reviewers), agencies may request a review of R/D documentation.

Despite this, many manufacturers keep relatively loose batch records in this phase, which prolongs the reconciliation process. If you are not having your analytical methods qualified early on, you are more likely to make errors that cause regulatory agencies to question your product's safety and efficacy. This is a frequent cause of the back-and-forth that adversely impacts timelines.

Here is a common myth: CMC guidelines are the end-all, be-all for forming regulatory checklists. However, the CMC is just a checklist of qualifiers that need to be submitted to the FDA. At this point, analytical qualification is phrased as a recommendation, not a requirement, which misleads many manufacturers into implementing looser standards that raise issues later.

Here is another myth: you are totally exempt from GMP during Phase I. While you are exempt from regulatory requirements at this stage, you are not exempt from statutory requirements. Although you do not have to have your processes and materials qualified, you do have to manufacture from a GMP facility. If you arrive at Phase I without GMP elements or a robust transition plan in place, you will lose money and time adjusting your protocols. Again, research phase is the best time to look ahead, anticipate needs, and take a proactive approach, where possible.

It is important to note that although earlier is better, there are also adversities associated with implementing GMP processes too early, as jumping the gun may restrict your ability to evolve. Choosing the right moment to implement is just as important as the implementation itself.

3. YOUR TOTAL REGULATORY FRAMEWORK

Knowing that early due diligence helps avoid costly consequences, it is worth investing time and resources into a comprehensive regulatory framework before or during the research stage.

From day one through market launch, your process and documentation methods – the heart of an effective regulatory framework – should offer you the flexibility to alter SOPs and materials quickly and effectively. Additionally, your framework should provide a clear overview of which GMP requirements are relevant to your product at every stage of development, considering the plethora of guidelines, white papers, and real-world case examples available today.

This helps your organization conduct a thorough gap assessment and make intelligent, proactive decisions. Ultimately, your framework should accomplish three things:

a. Develop key operating parameters and analytical methods that meet evolving regulatory requirements at every development stage

b. Integrate scientific standard of controls, process knowledge, risk analysis, and GMPs

c. Anticipate specific regulatory pushback, meet associated requirements prior to submission, and include rapid, decisive contingency plans where needed

Using this methodical approach, difficult technology transfers become much more manageable. Recently, the team at Cytovance Biologics worked with a client attempting to transfer a 20-year-old process to Phase III. As there are no established FDA guidance documents on producing protein drug substances using biotechnology specifically for phase III trials, we were tasked with learning how raw material attributes impacted the client's process productivity, yield, and quality (in lab, pilot, and GMP runs).

In the process of helping this client deliver their product to market, Cytovance integrated a wide range of industry guidelines and best practices to develop the **Product Development Lifecycle Matrix**, a fully comprehensive regulatory framework for biopharmaceutical manufacturers moving from research to clinical development. Using this framework, we help life science manufacturers chart a strategic course from TPP to commercialization, providing validated recommendations for equipment and control-, analytical-, and quality-driven initiatives.

EXCELLENCE FROM DAY ONE

While no two product lifecycles are the same, it is increasingly apparent that the longer manufacturers wait to make regulatory requirements a priority, the more they stand to lose. Whether you work with a CDMO or handle manufacturing in-house, it is crucial that your strategy includes a long view and proactive thinking.

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Implement a regulatory framework that provides value and positions your product for long-term success.

ABOUT CYTOVANCE BIOLOGICS

Cytovance® Biologics is a leading biopharmaceutical Contract Development and Manufacturing Organization (CDMO) that excels in the rapid and cost-effective development and manufacture of large molecule active pharmaceutical ingredients (APIs) from both mammalian cell culture and microbial fermentation such as monoclonal antibodies, fragment antibodies, bispecifics, enzymes, fusion proteins, vaccines and other biological products including plasmid DNA and cell-based therapeutics. In addition to our clinical and commercial CGMP API manufacturing services, Cytovance offers well-integrated development services supporting the entire product lifecycle including cell line development, cell banking, microbial strain development, process and analytical development, and process characterization. A centralized, responsive program management team coordinates all critical chemistry, manufacturing, and controls (CMC) activities for each client program around raw materials management, QC testing, ICH stability studies, and regulatory support. Our 140,000 sq. ft. state-of-the-art facilities in Oklahoma City is designed to meet U.S., EU, and other global regulatory standards.

Cytovance® offers deep industry expertise and unique customized services for the scale-up and cGMP manufacture of protein-based therapeutics; from early-stage pre-clinical development to commercial production, for both mammalian and microbial. Further information can be found at ***www.cytovance.com.***