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WHITEPAPER

Biologic drug products: A 5-point strategy for building a robust CMC dossier

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Abstract

Getting biological drug products to first-in-human (FIH) trials requires a deep and nuanced understanding of the scientific and regulatory challenges unique to these complex large molecule substances. Prioritizing regulatory CMC guidance and careful preparation of quality dossiers is integral to success from the very early stages throughout clinical development. This report identifies key strategies for developing a carefully executed, robust CMC dossier and avoiding common deficiencies that lead to clinical holds.

Executive Summary

The global market for biological drug products is expected to reach $749.62 billion by 2028, up from $324.78 billion in 2020, reflecting a CAGR of 10.80%.[1] And while small molecule drugs still dominate the pipeline, biologics, including cancer-fighting antibodies, vaccines, and gene therapy targets, account for more than 40% of the drugs in development, and their market growth is outpacing small molecules, with a CAGR of 11.4% over the past decade compared with 2.9% for small molecules.[2]

The appeal of biologics is their ability to interact with challenging therapeutic targets that small molecule drugs often cannot target, opening up new treatment avenues for patients with complex diseases while reducing the likelihood of off-target interactions that can lead to adverse effects.

With opportunity comes challenge, however. Because of their comparative complexity, biologics require a significant investment of time, money, and resources to manufacture. And there is inherently more risk in their development. Approximately 20% of biologic products experience delays or outright failure during late-stage development, translating to millions of dollars lost and delays to patient care.

Because speed to patients is the holy grail for biologics manufacturers, delays of any kind can be a significant setback. While some delays may be unavoidable, others, such as those incurred unnecessarily during the regulatory approval process, are fully preventable.

Both the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) have issued product quality guidance documents that address important CMC aspects, but no one guidance covers the exact playbook for a development program nor the CMC regulatory dossier. Innovators may not always know what is expected by the regulatory authorities or may decide to take calculated business risks in their early CMC planning, as they balance costs and speed to clinic with advancing product knowledge. To avoid clinical holds issued by the

health authorities that can impede submission approvals and the start of first-in-human (FIH) studies, they must also prioritize a deep understanding of regulatory CMC and careful preparation of quality dossiers, both of which are integral to success from the very early stages and throughout clinical development. For the FDA, the most common deficiencies leading to clinical holds are product quality issues, followed by clinical, and toxicology issues.[3]

This whitepaper discusses five strategies for building a robust CMC package to help streamline the path to FIH trials for biologics:

- Include regulatory CMC in early development teams
- Keep patient and clinical experience in mind
- Build a phase-appropriate dossier
- Consider and convey the basis for the strategy
- Obtain regulatory advice at every opportunity

By adopting these strategies, innovators can establish the quality foundation needed to support all of the development phases toward commercialization.

Introduction

Biological drug products are defined as products manufactured in, extracted from, or semi-synthesized from biological sources. By their very nature, these large molecule substances are inherently complex, and impart complex manufacturing requirements for cell culture, purification, aseptic processing, storage, and testing. The unique scientific, logistical, and regulatory challenges associated with these complex, large-molecule substances require sophisticated technology and controlled processes to move from preclinical to clinical development.

The FIH trial is the transition from study of a potentially promising therapeutic in the preclinical or animal setting to a small-scale study in people. The chemistry, manufacturing, and controls (CMC) regulatory dossier is the first opportunity to present CMC information to the regulator in a structured manner. At this stage the emphasis of clinical studies is primarily patient safety, so the CMC dossier should support how the early process and product knowledge relate to patient safety, thus enabling the investigational use in human clinical trials. These early human trials are important milestones as innovators aim to gain an understanding of drug safety, pharmacokinetics, and dose finding, which has been informed by the preclinical experience. As drug development progresses, the quality data and clinical experience from the FIH study begin to build product knowledge to inform future product development stages.

The following strategies for building a rigorous and thorough CMC dossier will help innovators get much-needed biological therapies to clinic as fast as possible while ensuring a safe, high-quality product.

Include regulatory CMC in early development teams

Bringing treatment options quickly into clinical trials is a key driver of a sponsor's timelines, and in intensely competitive environments this may translate into an accelerated development process. It is not unheard of that CMC development activities can sometimes be siloed and risk becoming out of step with the clinical planning. This has the potential to result in delays to achieving clinical objectives, particularly in smaller emerging companies with less drug development experience, or virtual companies that outsource all activities to multiple partners.

Building a rigorous and thorough CMC dossier will help innovators get much-needed biological therapies to clinic as fast as possible while ensuring a safe, high-quality product.

As a company prepares itself for a FIH study, the CMC and clinical planning for the molecule need to come together, each playing key and interdependent roles. This is why it's so important to get the CMC regulatory team member engaged right from the start. The objective is to have the required CMC elements of the FIH dossier at the same time the clinical team is ready to submit the proposed study protocol and the non-clinical data. Disconnects and surprises can occur when each function is not in regular communication with the other.

There are really two objectives for regulatory CMC at this stage. First is developing CMC regulatory strategies that enable the FIH dossier preparation and ultimately leads to regulatory clearance to enter the clinic. The second is to develop proactively considered strategies in order to progress through next phases of development without delays. For regulatory CMC this includes ensuring that required CMC activities that have long lead times are complete in advance of the planned IND/CTA submission timelines.

Regulatory CMC also supports clinical labeling by ensuring that activities that support the label are appropriately addressed in the CMC dossier. For example, it is not uncommon for clinical teams to want to maximize the hold time of prepared investigational drugs at the clinical site in order to optimize clinical operations.

Regulators require that in-use hold times are supported by appropriate compatibility study data to ensure chemical, physical, and biochemical stability over the hold period. Therefore, CMC study designs need to align with clinical in-use plans and results need to be included in the IND/CTA dossier.

The regulatory CMC team can provide valuable direction on agency expectations. For example, formulated biological products may be at risk to support microbial growth upon preparation, and in-use microbial studies for hold times greater than four hours may be required by some regulators. Regulatory CMC can assess what studies may be needed, interface with regulators on design when necessary, but ultimately ensure that the labelling is appropriately supported by the CMC dossier.

The regulatory CMC team member should also be part of the process to develop the pre-IND/pre-CTA briefing package. Study teams may express the desire to keep the focus of early interactions with regulators on the clinical program. But it is an opportunity missed if there's little to no early agency insight to the molecule itself and its CMC development plans. Clinical programs can be delayed, sometimes significantly. A solid pre-meeting briefing book should, at a minimum, provide an overview of the biological molecule, how it is made, a summary of its characterization to date and how this relates to the mode of action, the proposed clinical formulation and any available information on its stability. If you believe it's a standard manufacturing process, perhaps run on a platform, with no unique or novel operations, controls or other information of note, have your CMC regulatory team member contribute this in a summary. The benefit is that it enables the dialogue to switch over to the clinical program discussion, against the backdrop of this foundational CMC information.

In fact, there should be CMC regulatory representation by the late preclinical development stage, to support the linkage between the material used in toxicology trials and the FIH study drug. In the biological setting the active ingredient manufacturing process and the dosage form may already be representative of the intended clinical trial material.

Given the direct impact that CMC has on the overall clinical trial timelines, developing and integrating CMC strategies early in the development process is imperative, and for these reasons CMC regulatory should be an engaged partner of the core FIH team.

Keep the patient and clinical experience in mind

In the functional areas where drugs are manufactured and tested the predominant focus is product quality. The conversations are around potency, purity, consistency, and control. It is understood that the products will be used by patients and clinical trial subjects, but the connection between CMC data and clinical experience is sometimes lost. Quality attributes such as potency, purity, and batch-to-batch consistency serve an important role in informing the clinical experience, but conversely, the clinical experience helps justify the limits set for potency, purity, and consistency.

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As an example, the purity and potency of batches used in preclinical studies, including toxicology studies, provide insight to the safety of product that will eventually enter the clinic in the FIH trial. As the product moves into the clinic the limits for impurities must consider not just what the process is capable of to date but what it could mean clinically to the patient. If a process impurity is not adequately cleared, what would be the risk to the patient? What is the patient population, the condition being treated, other relevant concomitant conditions? Would the required limits on the impurity be different depending on the route of administration—for example, subcutaneous versus intraocular? When setting specifications, the process capabilities and test results can't eclipse the role of the product in therapy.

At the other end of the development lifecycle, when setting commercial specifications, there is the temptation to keep proposed specifications wide, ostensibly because manufacturing experience is still limited. But it is difficult to justify limits that are wider than the actual results of batches used throughout the clinical program. A good example is setting potency limits for cell-based bioassays. Although bioassays have a reputation for being "variable," in practice this isn't always the case. So it is difficult to justify a rather wide specification range if the bioassay used throughout development performed with significantly less variation, and all clinical trial batches were consistently close to the target. This is because there was no clinical experience at the upper and lower limits of the proposed range, so no patient received a drug that was that significantly less or more potent than targeted during the trials.

It's important to grow product and process knowledge starting in early development and build on that knowledge through subsequent product development stages. Biologics are large molecules produced in living systems and are structurally complex. Manufacturing changes, including process and formulation optimization, scale-up and site changes are common. These have the potential to introduce modifications to the molecule. Even minor structural differences (including certain changes in glycosylation patterns) can significantly affect critical properties of a biologic molecule (e.g., binding, solubility, potency, and immunogenicity), and consequently its safety and efficacy in clinical practice. The comparability exercise that compares product pre- and post-change likewise relates back to the patient and needs to consider not only specification limits but historical batches. If post-change material exceeds the limits set for analytical comparability, then again, the next step is to consider clinical relevance. Hence everything relates back to the patient.

Build a phase-appropriate dossier

The FIH IND/CTA dossier is the regulator's first opportunity for a comprehensive review of the chemistry and manufacturing of the study drug. It's important then to prepare a phase-appropriate dossier for this review. But what does this mean?

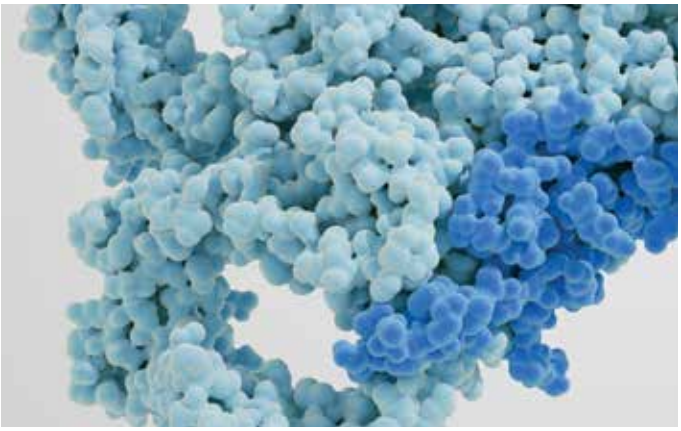
As a general rule for biologics, the strategy would be to report what you know. There will be information that is already established and should be included. This would include such things as robust descriptions of the cell line and expression construct, the initial cell bank, and any exposure to materials of animal origin. Information essential to evaluation of patient safety needs to be included, such as the evaluation of viral and adventitious agent safety. Information known to date about the molecule characterization should be included, and impurities discussed. The manufacturing process will be described with sufficient accuracy, but not in batch-record-like detail.

The key and critical process controls are not likely known yet. Specifications for release and stability testing should enable assessment of drug safety but other tests may not yet have defined limits and the criterion may be "Report Results." The test methods should be fit for purpose but not yet validated, and the reference standard should be developed. An appropriate amount of stability is needed at suitable storage temperature to support the filing and accelerated and stress conditions data are expected.

The FIH dossier is the first submission that shares product and process knowledge, and at that point the knowledge is understandably limited. However, one key recommendation is to take a very deliberate approach to enhancing knowledge of the product's critical quality attributes (CQAs) through development. CQAs inform everything from process development, manufacturing controls, and setting specifications to comparability exercises. Purposefully growing an understanding of CQAs of the molecule benefits decision making and problem solving through the product lifecycle.

In moving a promising drug candidate into the FIH clinical studies there is a driver to be nimble. Companies will focus on the must-have CMC activities and risk-assess the nice-to-have activities to meet often short timelines. Having a farther horizon for manufacturing development and CMC regulatory strategy can help prioritize phase data requirements, facilitate decision making and timing of regulator engagement, and ultimately mitigate delays.

It's almost certain that as the product moves from the FIH studies through the clinical development stages, significant changes to the CMC and CMC dossier will occur. These changes can include increasing scale to meet larger clinical trial studies and commercial capabilities, incorporating process optimizations to address increased process and product knowledge, changes to formulation and dosage forms to address patient solutions improvements, or introducing new regulatory jurisdictions for clinical studies, which may have their own regional regulatory nuances and CMC requirements. The list of possible changes is numerous and unique to any one development program. Embracing a forward-looking approach enables you to begin Chapter 1 of the "Regulatory Story" as the foundation to the next chapters.



A forward-looking view can facilitate dialogue with regulators, as it demonstrates a thoughtful approach to the product's development.

Anticipating the product development lifecycle includes thinking about future manufacturing capabilities. For example, evaluating whether the early phase manufacturing process may be difficult to scale up from an equipment and controls perspective. In the midst of the early phase trial, is it necessary to think that far along? What if the molecule doesn't progress beyond Phase I? There can be advantages to doing so, especially if it avoids introducing extra changes or more costly delays late in the development program to accommodate the increased scale. For instance, a company's early phase downstream manufacturing process employs a novel chromatography resin sourced from a single supplier. When predicting impact of scale-up to a commercial manufacturing scale, was there an evaluation of whether the supplier can reliably meet increased demand? If that evaluation identified a risk to supply of this critical material, what would the mitigation need to be and when would it need to be triggered?

Having a forward-looking view doesn't mean implementing all changes or risk mitigations upfront. But it does help in evaluating "now" versus "later" trade-offs and prioritizing CMC studies and investments, as well as phase-appropriate planning. For instance, mapping out when a cell-based bioassay will be required in place of a binding assay to test potency, or when a process-specific host cell protein assay would be expected will ensure that these tests are available when needed, taking into consideration their development time. A forward-looking view can also facilitate dialogue with regulators, as again it demonstrates a thoughtful approach to the product's development.

One approach we encourage is to think about potential future expansion into additional countries and jurisdictions. At the FIH stage, it very often is a single jurisdiction application. However, we strongly encourage two considerations.

The first is to write the CMC dossier in as jurisdiction-neutral a manner as possible. This means avoiding references to any specific regulator, or the guidelines of any specific country, and avoiding references to communications, meetings, minutes, or commitments to a given regulator in the body of the Quality Module. This "core dossier" approach really helps to make the CMC module reusable for a subsequent filing in a new jurisdiction, with minimal rework and faster preparation time.

The second consideration is to perform a thorough gap assessment of CMC requirements between the major jurisdictions of interest. A simple example is comparing compendial standards for raw materials, especially excipients. Some applicants discover these gaps as late as the marketing application preparation stage. At that point there is a scramble to evaluate the impact to the application, and potentially perform extra testing. Again, this isn't meant to suggest all gaps should be remediated at the Phase I development stage but rather to identify which gaps would have greatest effect on the timeline for entering subsequent jurisdictions.

At the FIH stage it may seem too soon to think about preparation for marketing applications. However, it is of value to consider which studies may only be done once in the product's development and therefore take the opportunity to consider collecting robust data upfront, in anticipation of the need for this data eventually. Examples are assuring the clonal nature of the master cell bank with high probability and end of production cell banking for the limit of in vitro cell age studies.

Engaging and leveraging the expertise of your manufacturing partner early on is another way to help identify CMC requirements for your FIH dossier, as well as to plan for next steps in the product development cycle. Discussing the process development lifecycle and assessing gaps prior to reaching pivotal stages of clinical development will help with the overall speed to commercialization.

Consider and convey the basis for strategy

When authoring a CMC regulatory dossier there are a couple of key objectives that should be kept in mind. The first objective is straightforward, and this is telling the reviewer the "what." The "what" focuses on, for example, how the biological product is being manufactured, the types of testing employed for release and characterization, and how stability will be demonstrated. The "what" comes from source technical documentation, and the level of detail necessary for the submission increases with the development phase, as the focus of the review progresses from safety to both safety and quality.

The second objective is authoring the dossier to tell the "why," or the basis of the manufacturing, testing, and control strategies and how this relates to the patient.

Although the regulator knows the science, it is the sponsor who is the expert on the product and its development history. When the "why" is poorly prepared, this may result in additional queries or clinical holds, and in the case of market applications, extending the review cycle and delaying approval times.

Meeting with regulators early in the development process is a critical step to advance a candidate into a FIH clinical study.

As a company's understanding of process and product knowledge progresses with development, it is expected that the basis for strategies described in the CMC dossier become more substantive and thoughtful. For instance, the approach to a release testing strategy in early development will be established with safety considerations in mind, with those safety tests having appropriate limits in place based on applicable guidelines. Other product-specific quality tests may have their acceptance criteria as "report only." As development progresses into the pivotal clinical stages and then onto a marketing application, the testing strategy and establishment of acceptance criteria becomes a more elaborate exercise by taking into consideration manufacturing experience, relationship to the molecule's critical quality attributes and clinical relevance.

Discussing the basis for CMC decisions should not be limited to justification of specifications. Many decisions are made throughout product and process development, yet it is not uncommon to find that the rationales for these are missing or unclear in a submission dossier. The "why" can be brief, especially in early development, but it demonstrates the thought process of the sponsor. Examples include the reason for selecting characterization tests (the nature of the molecule, its primary mode of action and potential other biological activity) and why the purification steps were chosen (based on expected impurities and their potential relevance). Even a brief rationale can convey that a decision was thoughtful and deliberate.

Take opportunities to obtain regulatory advice

Meeting with regulators early in the development process is a critical step to advance a candidate into a FIH clinical study. There are several reasons why meeting with the regulators can be beneficial to the development process. In early phase settings, a meeting provides an opportunity for the regulator to get to know the company and the molecule, and all within the context of the planned clinical program. Additionally, it allows for formal feedback to CMC strategies, including future development plans, thus benefiting from the experience of the regulator, their knowledge of the regulations, and in many cases their experience with similar products.

As noted, there are benefits to including the regulatory CMC representative on the FIH study team early in the process. By engaging early, the CMC content and strategy become an integrated part of the molecule's briefing package enabling the regulator to have the technical introduction to the molecule concurrent with its clinical development plan. Combining the CMC discussion with clinical/preclinical discussions at the FIH prefiling meeting can optimize FIH study readiness. There is the opportunity to gain alignment on the CMC content the regulator will expect in the dossier.

Where sponsors are uncertain as to interpretation of requirements, or atypical strategies are being proposed, this is the chance to ask questions. Our first question to customers is always, "Are you planning a pre-filing meeting where you can raise this for discussion?" In that respect, we encourage asking well-focused questions that will produce actionable answers. It's always recommended that the sponsor put forth their query in the form of a proposal and ask for agreement and feedback. It can be daunting at times to ask the hard questions that could have impact to the development program timeline and resources, but postponing the dialogue could have greater impact further along.

For expedited development programs, understanding the regulator's flexibility on the type, extent, and timing of certain manufacturing information and submission components, is paramount to the planning process.

Your manufacturing partner is also a resource for regulatory support and insight, especially for innovators who may have limited in-house regulatory resources or reach. It is now commonplace for full-service CDMOs to have regulatory consulting offerings made available to their customers to support regulatory needs and activities. Since a CDMO works with a diverse portfolio of molecules through different stages of the product development lifecycle, they can leverage a depth and variety of experience. In collaboration with the customer and the clinical program, this experience can help define strategies and optimize development efficiencies.

Taking the opportunity to obtain regulatory advice during the development process will help to identify and avoid potentially unnecessary development studies, while focusing resources and expenditures on those studies that are needed to progress development. By aligning with regulators and other experienced resources on CMC content and regulatory expectations, CMC-related clinical holds and potential costly delays to important milestones can be avoided.

Conclusion

The application to conduct the FIH clinical trial is the beginning of the regulatory lifecycle for a therapeutic molecule. It begins the information sharing for the molecule's CMC which then continues through development, commercialization, and into the post-approval maintenance stage. Involving Regulatory CMC early enables building a phase-appropriate dossier with a forward-thinking strategy. Optimizing the beginning of that journey by leveraging scientific advice from regulators and expertise from your CDMO partner removes obstacles on the road to the clinic and can establish the supportive framework for subsequent development phases toward commercialization.

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