Note: Demystifying, according to Merriam-Webster’s dictionary, is “to remove the mystery or mystique; to make rational or comprehensive.” This is the third part of a series on demystifying CMC regulatory strategy for biologics. Part 1 covered the complexity of biologic CMC regulation; Part 2 examined the major differences between biologics and chemical drugs; and Part 4 will examine the challenge of adventitious agent contamination control for biologics.

Failures in the chemistry, manufacturing and controls (CMC) regulatory strategy for biologics abound: a recombinant enzyme is delayed in gaining market approval because the US Food and Drug Administration (FDA) concludes that “the commercial process is not representative of the Phase 3 material used to establish the safety and efficacy profile;” a recombinant protein is rejected by the European Medicines Agency (EMA) because “with regard to Quality a large number of outstanding issues remained” (e.g., lack of product comparability, insufficient stability data, manufacturing process not adequately validated); a recombinant protein is withdrawn from the US market because a “minor change in the formulation” leads to spontaneous syncope (fainting).

When it comes to CMC regulatory strategy for biologics, maybe Mike Tyson, former world champion heavyweight boxer, got it right: “everybody’s got plans...until they get hit.”

Strategy is the course of activities that leads to a defined objective (for CMC regulatory strategy, the objective could be initiating Phase 1 first-in-human clinical studies, obtaining market approval, etc.). Defining the corporate CMC regulatory strategy is a first step (although reaching a consensus on what that strategy should be is never easy).
However, the more challenging step is ensuring that the defined corporate CMC regulatory strategy is also effective, not wasting limited CMC resources for biologics.

### Shaping Forces

Historical, financial and personal realities are intertwined in any corporate strategy. But the two major forces that shape corporate CMC regulatory strategy for biologics are risk tolerance and resource allocation.

#### Risk Tolerance

When we consider the individuals involved—manufacturing, quality and regulatory staff and senior managers—the assignment of risk (i.e., the severity and probability of harm) to each of the various CMC regulatory activities in the strategy will be perceived differently. The combined subjective determinations result in the corporate culture of risk tolerance.

Some corporations, particularly those with only a single biopharmaceutical, have to be CMC risk takers, primarily due to minimal finances for survival and little time to spare due to competition. Other corporations, especially if profitable, can afford to weigh CMC risks more carefully and be much less tolerant of CMC risk.

Managing this risk tolerance can seem like the familiar Aesop fable, “The Hare and the Tortoise.” On the one hand, the CMC regulatory strategy like the Hare appears designed to move too quickly: Just keep the project moving forward and fill in the missing CMC activities at a later date.

On the other hand, the CMC regulatory strategy like the Tortoise appears designed to plod along operating at low to no risk: “Slowly does it every time!” exclaimed the Tortoise.

An effective CMC regulatory strategy for biologics, like neither the Hare nor the Tortoise, keeps the project moving forward at an acceptable pace that does not place patients in danger and succeeds in doing it right the first time.

#### Resource Allocation

Not enough resources and not enough time are the familiar laments of those who manage the biologic CMC regulatory strategy. Extra resources are necessary to meet the activities of an effective biologic CMC regulatory strategy (see Table 1).
Biologics are complex products made using complex living system manufacturing processes. Their greater CMC resource requirements must be factored into the corporate budget.

Typically, though, annual budget discussions with senior management set the stage for increased CMC risk taking. The question is usually something like: “For this biologic, what CMC activities can be postponed until later?” The intent is very clear in these budget discussions and can be considered justifiable in this era of being cost effective.

However, the question could be better phrased: “For this biologic, what CMC activities can be postponed until later without incurring an unacceptable CMC risk to the project and the patients?”
Three Major Elements
An effective corporate CMC regulatory strategy for biologics must include three major elements: (1) inclusion of all CMC regulatory activities, (2) provisions for any unique CMC regulatory requirement for specific biologic groups and (3) alignment of the strategy with International Conference on Harmonisation (ICH) Q8/Q9/Q10 guidance.

Embrace All CMC Activities
CMC means activities related to chemistry (product characterization, product release and stability testing), manufacturing (manufacturing facility, utilities, process equipment and materials, manufacturing personnel, manufacturing process) and controls (in-process controls, product specifications, product expiration dating, documentation, batch record review, auditing).

The complete list of CMC activities and their timing for completion vary widely with the biologic manufacturing process and the biologic produced; for example, the genetically engineered cell culture-produced monoclonal antibody in a stainless steel bioreactor followed by extensive purification (see Figure 1a) versus the short-lived patient-specific autologous cellular therapy manufacturing process with no purification (see Figure 1b). A “big-picture” view of all CMC activities and the intended timing for their completion allows the strategy to be adjusted as needed, either to address delays in CMC forward progress or gaps in needed CMC resources.

Address Unique Requirements
All biologics are not alike, and due to the diverse living systems used to produce them, each has specific safety concerns that must be addressed in an effective CMC regulatory strategy. For example:

- Immunogenicity due to carbohydrate: Bacterial cell lines produce biologics with no carbohydrate; yeast cell lines produce biologics that can have large mannan structures; plant cell lines produce biologics that can have bisecting β(1-2)Xyl on the β-linked mannose structures.
- Adventitious agent contamination: Bacterial, yeast and plant cells are not susceptible to viral or mycoplasmal infections; insect, animal and human cells have a wide susceptibility to both viral and mycoplasmal infections.
- Replication competency: Genetically engineered viruses, whose genetic element of replication has been removed, are used in gene therapy; however, when the viruses are propagated on animal or human cells, they are capable of recombining their lost replication capability, presenting a significant safety risk to patients.
- Prions: Human donors are the source of plasma-derived proteins and human-sourced biologics carry the highest risk for prions (e.g., Creutzfeldt-Jakob disease).

Table 2. Recent ICH Strategic Guidances

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<th>ICH Q8, Pharmaceutical Development (2005): “To design a quality product and its manufacturing process to consistently deliver the intended performance of the product.” The guidance introduces the concept of Quality by Design (QbD), which is “a systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk assessment.”</th>
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<td>ICH Q9, Quality Risk Management (2005): “A systematic process for the assessment, control, communication, and review to the quality of the drug product across the product lifecycle.” The guidance encourages the use of recognized risk management tools such as Failure Mode Effects Analysis (FMEA), Preliminary Hazard Analysis (PHA), etc.</td>
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<td>ICH Q10, Pharmaceutical Quality System (2008): threefold focus: (1) Achieve product realization (“establish, implement, and maintain a system that allows the delivery of products with the quality attributes appropriate to meet the needs of patients, health care professionals, regulatory authorities”), (2) establish and maintain a state of control (“develop and use effective monitoring and control systems for process performance and product quality, thereby providing assurance of continued suitability and capability of processes”), and (3) facilitate continual improvement (“identify and implement appropriate product quality improvements, process improvements, variability reduction, innovations, and pharmaceutical quality system enhancements, thereby increasing the ability to fulfill a pharmaceutical manufacturer’s own quality needs consistently”).</td>
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ICH has provided invaluable guidance on CMC content for biologics for almost a decade (see the Q5 series at www.ich.org). But more recently, a series of new ICH strategic guidelines that impact the biologic CMC regulatory strategy has been issued (see Table 2).

These guidances are not just for chemical drugs but also for biologics, as ICH Q10 states clearly: “This guidance applies to the systems supporting the development and manufacture of pharmaceutical drug substances (i.e., active pharmaceutical ingredients (APIs)) and drug products, including biotechnology and biological products, throughout the product lifecycle.”

ICH Q11, Development and Manufacture of Drug Substances (2011 draft), provides numerous examples illustrating how these new strategic ICH guidances can be applied to biologics (see Figure 2). While this illustration looks impressive and is very scientifically instructive, the amount of science presented comes only with a major investment in experimentation.

Unfortunately, good science comes at a price and this is where senior managers must consider how they can support these efforts by providing adequate resources to carry out these studies on the biologic during the development period. After all, what is the alternative to quality by design (QbD)? Quality by chance (QbC) is not a good option.

According to a recent FDA-commissioned study, QbD has been making significant inroads in the biologics industry, with 17% of the biologic companies surveyed indicating that they were already using QbD principles regularly and 67% indicating that they were trying QbD principles. A conclusion from that study indicated the following:

“Although many manufacturers site [sic] QbD as being impossible, especially with upstream processes—our interviews indicate this is not true. Many biologics manufacturers are applying QbD to downstream processes with great results. These manufacturers believe that QbD is even more important for biologics as the molecules are more complex and a deeper understanding will lead to better product. There is no reason why QbD should not apply to biologics. The FDA should continue to be patient, disseminate success stories, and hold forums concerning QbD for biologics companies. Over time, the case for QbD for biologics will become increasingly clear.”

Figure 2. Illustration of QbD Applied to a Q-Anion Exchange Chromatography Step

Figure presented in ICH Q11 (draft) to illustrate process-related impurities removal during the purification of a monoclonal antibody; white boxes on the right reflect adequate individual process-related impurity removal; and the white box on the left reflects a design space where satisfactory viral clearance, host cell DNA and host cell proteins can all be achieved; available at www.ich.org.
Today, we are expected to defend our CMC regulatory strategy for biologics using risk-managed, scientifically sound justifications, not preset industry-standard arguments.

Clinical Phase-dependence

Clinical phase-dependence is defined as ‘matching the extent of completion for a CMC activity, as well as the timing for its completion, to the patient safety risk associated with each clinical development phase.’

In applying clinical phase-dependence, the amount of committed effort for each CMC regulatory activity is “weighted” to the patient risk associated at each clinical development phase, with more CMC effort committed at later clinical development stages (e.g., Phase 3 confirmatory study to determine that a drug is safe and effective for use in the intended indication) than at earlier clinical development stage (e.g., Phase 1 human pharmacology study with healthy volunteer subjects).

Clinical phase-dependence can serve as an effective relief valve from the pressures of changing risk tolerance and limited resources. And, for biologics, it is accepted by the regulatory authorities.

FDA Embracement

FDA permits considerable flexibility in the amount and depth of CMC data required to be submitted for all pharmaceutical products. Title 21 of the Code of Federal Regulations (CFR), Part 312.23(a)(7), provides an example of this flexibility: “For example, although stability data are required in all phases of the IND to demonstrate that the new drug substance and drug product are within acceptable chemical and physical limits for the planned duration of the proposed clinical investigation, if very short-term tests are proposed, the supporting stability data can be correspondingly limited.”

FDA reinforces its acceptance of a clinical phase-dependent CMC regulatory strategy for biologics with statements in several regulatory guidances:

- Monoclonal Antibodies
  “It is not necessary to have all of the information discussed in this document available in the initial IND submission. Rather, much of the information may be developed during the clinical development....”

- Gene Therapy Biologics
  “A. Development of Release Acceptance Criteria
  We recommend that proposed release acceptance criteria for the final product be based on scientific data and manufacturing experience obtained during development of the product as described below:
  • Phase 1—Based on data from lots used in preclinical studies.
  • Phase 2—Refine and tighten based on data generated during Phase 1.
  • Phase 3—Based on information collected during product development.
  • Licensure—Based on information collected during product development using validated assays.

B. Development of Acceptance Criteria Analytical Procedures
We recommend that proposed analytical procedures be based on scientific data and manufacturing experience as described below:
  • Phase 1–3—Usually based on Code of Federal Regulation (CFR) methods or alternative methods, if appropriate.
  • Phase 2—if an alternative to the CFR method is used, we recommend that the sponsor initiate validation of the alternative by Phase 3.
  • Licensure—The product specification should be in place and established under a validated assay.

C. Development of Stability Protocols
In order to develop adequate stability data for timely submission in a license application, we recommend that a sponsor implement and expand the stability program as described below:
- Phase 1–3—Preliminary data on product stability must indicate whether the product or components are likely to remain stable for the duration of the clinical trial. Note: the regulations require that the IND contain these data at each stage of the clinical trial (21 CFR 312.23(a)(7)(ii)).
- Phase 2—We recommend that the sponsor initiate a stability protocol to accumulate additional data.
- Phase 3—We recommend that the sponsor begin to establish the dating period, storage conditions, and shipping conditions based on data derived from the stability protocol.

**EMA Concurrence**

EMA acceptance of the clinical phase-dependent CMC regulatory strategy for biologics is stated in a recent regulatory guidance entitled, *Guideline on Quality Documentation Concerning Biological Investigational Medicinal Products in Clinical Trials.*

“The extent of the information required for an IMP Dossier (IMPD) should take into account the nature of the product, the state of development/clinical phase, patient population, nature and severity of the illness as well as type and duration of the clinical trial itself. When compiling the quality part of the IMPD for phase II and phase III clinical studies, the wider exposure of patients to the product and the progressive product knowledge have to be taken into account compared to phase I clinical studies.”

“Because the acceptance criteria are normally based on a limited number of development batches and batches used in non-clinical and clinical studies, they are by their nature inherently preliminary and may need to be reviewed and adjusted during further development. Additional information for phase III clinical trials: As knowledge and experience increases, the addition or removal of parameters and modification of analytical methods may be necessary. Specifications and acceptance criteria set for previous phase I or phase II trials should be reviewed and, where appropriate, adjusted to the current stage of development.”

**One Size Does Not Fit All**

A one-size-fits-all approach does not work for biologic CMC regulatory strategy. The CMC strategy must be tailored to fit the corporate culture of risk tolerance and available resources. In addition, it must be adjusted according to an appropriate and adequate clinical phase-dependent plan.

While the clinical phase-dependent approach has advantages in resource conservation, it can pose a major danger: postponing certain CMC regulatory activities to later clinical phases can result in forgetting that those CMC activities must still be accomplished. This is especially a concern with so much movement of staff in and out of biologic companies.

Thorough documentation of the decision-making process must be made available to future CMC teams to remind them of the need to complete those delayed CMC activities.

**References**


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