Q&A

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Chemistry, Manufacturing and Controls (CMC) continues to be one of the most critical aspects of drug development. Recent FDA data highlight just how significant the impact can be: in July 2025 alone, 202 Complete Response Letters (CRLs) were issued, with nearly three quarters citing CMC-related deficiencies. While many of these issues are often viewed as isolated technical gaps, they frequently point to a deeper challenge in how CMC is approached and executed across development programs. To better understand the root causes behind these trends and how developers can address them, we spoke with Amy Glekas, Ph.D., Senior Director, Global Head of Field Development at Solvias. In this Q&A, she shares her perspective on the systemic nature of CMC challenges and offers practical insights on how teams can stay aligned and keep their programs on track.

Q **In 2025, the FDA published complete response letters (CRLs), and CMC issues were a major cause. Why do you think that is?**

Our team has been analyzing those CRLs, and in fact, 74% of the 202 CRLs published in July 2025 cited CMC deficiencies. We saw recurring issues: extractables and leachables, CCIT, method validation, and we've even published white papers addressing each of them, with more coming. But when you step back, it's not just about isolated technical gaps. It points to a broader, systemic issue in how CMC is approached.

Q **What do you mean by a systemic issue?**

Many sponsors treat CMC as if they're outsourcing pieces of a puzzle, assuming that if each partner delivers their part, everything will fit together in the end. But when those pieces are designed in isolation, they rarely do. One team may focus on structural characterization, another on potency, another on impurities. Each generates valuable data, but frequently, no one is actually assembling the full picture as data are being generated. So when regulators ask detailed questions, teams are left trying to force those pieces together, often under pressure, instead of dedicating appropriate time and expertise to interpreting the data globally and presenting a coherent story. The reality is that CMC isn't about collecting pieces. It's about understanding how they connect from the start. Every decision is interdependent. Your cell line affects your process, your process affects your analytics, and your analytics ultimately shape your regulatory strategy.

Q **It sounds like a fragmentation problem more than a scientific one. Is that how you see it?**

To some extent, yes. The science is, of course, challenging, and the level of expertise required to analyze increasingly complex therapeutic modalities, along with evolving regulatory expectations, is only getting higher. But the challenge isn't just the science, it's managing how everything interacts. We see this all the time with analytical methods, for example, especially when early-stage methods are not designed with late-stage robustness and throughput in mind. Analytical development may occur in one group, validation and transfer in another, routine, early-phase QC in a third, and late phase readiness activities somewhere else. Over time, small disconnects accumulate, and continuity across the method lifecycle becomes difficult to maintain. The version of the method developed is not always identical to the version ultimately validated. The validated version may differ subtly from the version transferred or routinely executed in QC. Such inconsistencies can become critical during regulatory review and may be interpreted by regulators as evidence of inadequate method lifecycle management.

Q **Misalignments like that become obvious to regulators at the NDA or BLA stage, right?**

If you get that far, right? I mean, many programs start to drift well before that. Not because of a single bad decision, but from a gradual loss of alignment. Different teams making reasonable decisions, but without a shared reference point. Add in scale-up, tech transfer, or evolving regulatory expectations, and the program can start to diverge from its original path. And once that kind of drift sets in, it's not something you can fix with a single course correction. That's why alignment early on is so critical. As programs advance, you're generating more information, across more dimensions, with higher expectations for consistency and justification. If that complexity isn't grounded in a shared understanding, it becomes harder and harder to interpret the data in a way that supports clear, confident decisions. But when alignment is anchored in reliable, well-integrated data, teams can navigate that complexity and stay on track. That consistency is what ultimately allows programs to move forward and bring therapies to patients.

Q **What can teams do to ensure alignment and avoid drifting over time?**

It starts with how teams think about analytics. It can't be treated as a checklist item. It has to be part of the strategy, from preclinical development all the way through commercial release. At Solvias, we support developers with our analytical capabilities that generate reliable, complete, and decision-ready data to enable alignment and informed decision making. These data become especially important at moments of uncertainty, whether during transitions, scale-up, or evolving regulatory expectations. When alignment is anchored in reliable data, teams are better equipped to navigate uncertainty and stay focused on their goals.

What FDA CRLs Reveal: A White Paper Series

As Amy mentioned, since the FDA began publishing CRLs, we've been analyzing them to uncover where drug applications fall short and how to avoid the same pitfalls. The result is a growing library of white papers translating real regulatory feedback into actionable insights. So far, we have launched three white papers, each addressing critical areas of regulatory scrutiny: Extractables and Leachables (E&L), Container Closure Integrity Testing (CCIT), and Method Validation. Unlock the series and access practical recommendations grounded in real FDA feedback.

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