Why You Can't Design a Prefilled Syringe System Out of Components

Over decades, the challenges of drug delivery have continually been met with innovation. Problems have been met with solutions.

Take the prefillable syringe. These devices were first introduced in the Second World War as a mechanism for delivering injections in battlefield settings – an innovative answer to the question of how to administer medication with speed, sterility and dosing accuracy. While the fundamental premise has remained the same, today prefilled syringes have grown in significance and prevalence, with advances in design and materials science ensuring they have a crucial role in the delivery of drugs, including sensitive biologics, through their ability to preserve the drug's quality, efficacy and safety; deliver highly targeted doses; and support self-administration.

While prefillable syringes might have provided the means to simplify drug delivery, they are part of a highly complex, strongly regulated, and traditionally component-driven development program. Being regulated as combination products adds an additional layer of complexity. From design and development through part selection, design and development verification and manufacturing, there are many critical, often contradictory considerations that must be taken into account to simultaneously ensure the quality, efficacy and safety of the drug within a safe, functional and usable device. The success of these development programs is undoubtedly testament to the sector's problem-solving capabilities, but they also serve to highlight the absence of more efficient 'top down', integrated and holistic solutions.

The issue at the heart of the matter is that while prefillable syringes present as systems, they are, in fact, as of now a collection of multiple components combined to form a coherent whole. And given the highly regulated nature of these combination products, it is therefore quite typical for development to be a lengthy and highly complex process. In a market increasingly populated by emerging biotechnology companies, the process of taking a molecule from formulation to the market as a final combination product can be a daunting one, beset with pressures in a variety of areas.

Currently, these issues are addressed through engagement with external consultancies and a disaggregated network of supply chain partners. The onus is on the drug originator to co-ordinate these moving parts and bring various strands of development together. Indeed, the sourcing and procurement of components demands detailed knowledge of the quality target product profile (QTPP), the critical quality attributes (CQAs) and other information needed to create robust design and development inputs as guided by the Quality Guidelines 8 and 9 of the Internation Council of Harmonization (ICH Q8 and Q9).[1] Current Good Manufacturing Practice (cGMP) regulations across global territories, which include Part 211 (Current Good Manufacturing Practice for Finished Pharmaceuticals) and Part 820 (Quality Management System Regulation) of Title 21 of the Code of Federal Regulations in the United States (21 CFR Part 211 & 820) and the GMP guidelines in the European Union (EU GMP).[2,3,4]

In the very earliest stages of defining the design and development inputs and selecting the according components, pharma and biotech companies looking to develop a prefillable syringe (PFS) system face an almost bewildering array of component choices. And for each component, arriving at an optimal decision will require engagement in a time-consuming and highly detailed sourcing process involving multiple contacts at a broad range of potential supply partners. Typically, this will initially involve stakeholders defining the component specification before conducting market research to identify possible candidate suppliers. Following completion of this phase, requests for information (RFI) will be issued to shortlisted providers as part of an evaluation of production capabilities and to verify quality and compliance credentials. Risk assessments and supplier qualification checks will also need to be carried out as part of this comprehensive due diligence process, which for each company will need to be conducted under the security of a Confidential Disclosure Agreement (CDA) to ensure all parties are legally protected. Indeed, in some cases, there will be a need to establish more complex three-way CDAs to facilitate discussion between multiple partners.

Taken together, all these stages evidently add up to a significant investment in time, energy and therefore cost for sponsors, who are ultimately responsible for oversight of the device. They face clear pressure in managing supplier relationships effectively and mitigating risk in the interests of final drug quality and continuous improvement. Importantly, this must be considered from first point of engagement through to development, design and development verification and validation testing, clinical and human factor studies, technology transfer and commercial manufacturing, while also exerting control over change management activities and product quality throughout the combination product's lifecycle. Throughout, the need to align on technical demands must be matched by a shared culture, agreed behaviours and effective communication for this to be achieved with minimal friction.

Record-keeping and data management can present particular challenges in this multi-stakeholder environment. Sponsors are not only required to evaluate distinct device constituent part-level datasets in isolation, but – being a combination product – also to ensure performance of the PFS as a final system. Ultimately, disparate datasets will need to be compiled into a unified and robust Device and Development File (D&D File) as part of the submission as an Electronic Common Technical Document (eCTD).

Practically speaking, this task is far from straightforward. Take, for example, the fact that a rigid needle shield (RNS) will be supplied with product specifications detailing material attributes across a variety of characteristics. This includes measurements such as pull-off force, endotoxin level, bioburden level and particulate matter – which are reported differently throughout the industry, e.g. according to a Proved Clean Index value. The same PFS system will also feature particle data from the glass barrel

supplier reported as a specific percentage based on United States Pharmacopeia-National Formulary (USP-NF) <788>.[5]

Meanwhile, the plunger supplier will report on particulate matter in terms of amount per square centimetre of plunger surface area. This places the onus on the applicant to understand the interplay between three different measures, potentially from three separate suppliers, in order to arrive at a robust singular evaluation of particle characteristics at a system level. And this is a task that must be repeated for all critical characteristics of the PFS beyond particulates, amounting to a heavy data-evaluation burden.

There are also inherent challenges regarding stakeholder management where multiple vendors are concerned, each with individual stipulations in terms of minimum order quantity options, and with limited guarantees of consistency when it comes to manufacturing processes and, therefore, quality. Moreover, if complaints later arise in relation to the PFS, accountability cannot likely be attributed to a single supplier, requiring the authorisation holder to detangle and resolve potentially difficult interlinked issues.

Assuming they are not 'show stopping', such challenges can, of course, be overcome, but resolving them can add layers of complexity and place additional demands on internal resource. If problems escalate, however, there is a real risk of milestones being missed, unforeseen increases in development costs and, potentially, delays to product launch. This might be caused, for example, by the need to retrospectively source specific aspects of performance data, the failure to meet in-clinic targets for quality and/or quantity of supply, or delays to the regulatory approval process.

Delays to a device's development schedule and launch are well known to have damaging implications. However, translating those problems into a financial cost has come down to estimates and anecdotal evidence. But in late 2023, the Tufts Center for the Study of Drug Development grounded this conversation in real-world figures based on empirical research. It concluded that the cost of missing a single day in drug development equates to approximately $500,000 in lost prescription drug or biologic sales. It also puts an approximate price tag of $40,000 per day on phase II and III clinical trials, underlining the financial imperative of avoiding issues that have the potential to extend trial schedules.[6]

For years, this fragile dynamic has been the status quo in the sourcing of prefillable syringes, driven by a component-based approach to device selection and evidencing of system-level performance. But zooming out to reflect on this situation, it is not unreasonable to question whether drug companies should continue to absorb these pressures as an accepted and unavoidable cost associated with achieving their goal. In an evolving market, is a one-size-fits-all approach optimal for all innovators? Where it is appropriate for the application in question, would it not be possible instead to bypass the many points of friction involved in building a system from disparate components and instead employ a ready-made system that has already been verified for the task?

Today, those assumptions are being directly challenged by the groundbreaking introduction of integrated PFS systems. Incorporating pre-verified device constituent parts – syringe barrel, plunger and needle shield/tipcap – these novel systems provide a catalyst for emerging biologic and vaccine innovators to accelerate the journey towards the critical milestone of clinical fill/finish. They provide the means to accelerate PFS selection, simplify vendor management, secure reliable single-source device supply, and streamline regulatory submissions through a pre-prepared system performance verification data package.

Applying a system-level approach such as this truly has the potential to shift the current paradigm in PFS development. As explored above, the current component-driven model introduces the need for sponsors to manage a multiplicity of risks across a disaggregated network of suppliers, which, cumulatively, can represent a potentially insurmountable task for emerging biotechnology companies that are under pressure to deliver their molecule to clinic and progress towards marketing approval.

As with so many examples of impactful innovation, the premise of taking a system-level rather than component-driven approach to PFS development is not reflective of wholesale reinvention or the ripping up a proven playbook. Rather, it is about challenging the status quo, addressing underlying flaws, and creatively rethinking how to optimise the pathway to same destination. It rests on an acknowledgement that where problems remain unsolved, drug delivery's innovators will keep rising to the challenge of pioneering newer, better, and faster ways of bringing therapeutic benefits to the lives of patients in need.

REFERENCES

1. ICH Guidance for Industry Q8: Pharmaceutical Development; International Council for Harmonisation (2009); ICH Guidance for Industry Q9: Quality Risk Management; International Council for Harmonisation (2005)
2. https://www.ecfr.gov/current/title-21/chapter-I/subchapter-C/part-211
3. https://health.ec.europa.eu/medicinal-products/eudralex/eudralex-volume-4_en
4. https://www.fda.gov/medical-devices/quality-system-qs-regulationmedical-device-current-good-manufacturing-practices-cgmp/quality-management-system-regulation-final-rule-amending-quality-system-regulation-frequently-asked
5. USP <788> Particulate Matter in Injections; United States Pharmacopeia (2013)
6. https://link.springer.com/article/10.1007/s43441-024-00667-w

Dr. Bettine Boltres

Dr. Bettine Boltres,Director Scientific Affairs, Integrated Systems at West Pharmaceutical Services, is a recognised thought leader in the industry, fostering scientific exchange between West and the pharmaceutical sector. She possesses extensive knowledge in glass, polymer, and rubber materials, which carries over in her expertise in combination products. Dr. Boltres is the author of the book "When Glass Meets Pharma" and serves as an expert for the United States Pharmacopeia (USP), European Pharmacopoeia (Ph. Eur.), and various ISO working groups. Additionally, she plays an active role in the Parenteral Drug Association (PDA) and is serving on the PDA Board of Directors since 2019.