WHY YOU CANNOT DESIGN A PREFILLED SYRINGE SYSTEM OUT OF COMPONENTS

Dr Bettine Boltres at **West Pharmaceutical Services** unravels the complexities of bringing a new molecule to market as part of a combination product and rethinks the way that drug-device design could be tackled instead, approaching the system as a whole rather than through individual component development.

Over the decades, the challenges of drug delivery have continually been met with innovation. Problems have been met with solutions. Take prefilled syringes (PFSs) as an example. These devices were first introduced during 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 PFSs have grown in significance and prevalence. Advances in design and materials science ensure that they play a crucial role in the delivery of drugs, especially sensitive biologics, through their ability to preserve the drug's quality, efficacy and safety; deliver highly targeted doses; and support self-administration.

NAVIGATING THE REGULATORY LANDSCAPE

While PFSs might have provided the means to simplify drug delivery, they are part of a highly complex, strongly regulated and traditionally component-driven development programme. Being regulated as combination products adds an additional layer of complexity. For design and development through part selection, 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 a drug within a reliable, functional and usable device. The success of these development programmes 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 navigating regulatory processes while simultaneously developing numerous components into a combination product. It is therefore 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, with significant challenges.

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, critical quality attributes and specialised information to create robust design and development inputs. These are guided by:

- Quality Guidelines Eight and Nine of the Internation Council of Harmonisation (ICH Q8 and Q9)
- GMP regulations across global territories, which include:
  - Part 211 (CGMP for Finished Pharmaceuticals)
  - Part 820 (Quality Management System Regulation) of Title 21 of the Code of Federal Regulations in the US (21 CFR Parts 211 & 820)
  - GMP guidelines in the EU (EU GMP).

STAGES OF PFS DEVELOPMENT

In the very earliest stages of defining the design and development inputs for a PFS, pharma and biotech companies face an almost bewildering array of component choices. For each component, arriving at an optimal decision will require engagement in a time-consuming and highly detailed sourcing process. This involves multiple contacts from a broad range of potential supply partners. Typically, this process will initially require stakeholders to define the component specification before conducting market research to identify possible candidate suppliers. Following completion of this phase, requests for information will be issued to shortlisted providers as part of an evaluation of production capabilities and 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. For each company, this will need to be conducted under the security of a Confidential Disclosure Agreement (CDA) to ensure all parties are legally protected. Furthermore, 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 overseeing 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 the first point of engagement throughout development, design and development verification and validation testing, clinical and human factors studies, technology transfer and commercial manufacturing. This must all occur while also exerting control over change management activities and product quality throughout the lifecycle of the combination product. Finally, 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.

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> "IN THE VERY EARLIEST STAGES OF DEFINING THE DESIGN AND DEVELOPMENT INPUTS FOR A PFS, PHARMA AND BIOTECH COMPANIES FACE AN ALMOST BEWILDERING ARRAY OF COMPONENT CHOICES."

Record-keeping and data management can present particular challenges in this multi-stakeholder environment. Sponsors are not only required to evaluate part-level datasets of device components in isolation, but must also ensure performance of a PFS as the final combination product. Ultimately, disparate datasets will need to be compiled into a unified and robust device and development file as part of an electronic common technical document submission to regulatory bodies.

FURTHER CHALLENGES IN PFS DESIGN

Practically speaking, this task is far from straightforward. Take for example, the fact that a rigid needle shield will be supplied with product specifications detailing material attributes for a variety of characteristics. This includes measurements such as pull-off force, endotoxin level, bioburden level and particulate matter – which at West is uniquely reported 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 US Pharmacopeia-National Formulary (USP-NF) General Chapter 788. 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. 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 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.

Such challenges can be overcome, but resolving them can place additional demands on internal resources. 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 or quantity of supply, or delays to the regulatory approval process.

Delays to the development schedule and launch of a device are well known to have damaging implications. However, translating those problems into a financial cost in the past has stemmed from 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 US$500,000 (£370,000) in lost prescription drug or biologic sales. It also puts an approximate price tag of $40,000 per day on Phase II and III trials, underlining the financial imperative of avoiding issues that have the potential to extend trial schedules.[1]

"APPLYING A SYSTEM-LEVEL APPROACH TRULY HAS THE POTENTIAL TO SHIFT THE CURRENT PARADIGM IN PFS DEVELOPMENT."

CHALLENGING ASSUMPTIONS

For years, this fragile dynamic has been the status quo in the sourcing of PFSs, driven by a component-based approach to device selection and evidencing of system-level performance. Taking a moment 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 appropriate, 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 questioned by the groundbreaking introduction of integrated PFS systems. By 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-planned system performance verification data package.

CONCLUSION

As discussed, the current component-driven model introduces the need for sponsors to manage a multiplicity of risks across a disaggregated network of suppliers. Cumulatively, this 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. Applying a system-level approach truly has the potential to shift the current paradigm in PFS development.

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 rewriting the rules. Rather, it is about challenging the status quo, addressing underlying flaws and creatively rethinking how to optimise the route to the same destination. It rests on the knowledge that where problems remain unsolved, drug delivery innovators will keep rising to the challenge of developing newer, better and faster ways of bringing therapeutic benefits to the lives of patients.

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