

Current Trends in Formulation Development and Implications for Drug Delivery Devices

The market for parenteral drug device combination products has been evolving over the last 15–20 years, developing innovation both on formulation and device design fronts. This change is driven by a series of factors including: the growth of biologics and biosimilars, predicted to increase at a compound annual growth rate (CAGR) of 23% from 2019 to 2027;¹ evolving healthcare systems in need of affordable therapeutic options; the rise in self-administration and an increasing focus on patient and user experience.

The key priority in formulation development is to create a cost-effective drug with proven efficacy and safety that can be scaled up for manufacturing. However, more recently the focus has shifted towards patient experience and ease of use. This change is in part driven by the increase in self-treatment outside the acute care setting to treat a variety of chronic conditions via an increasing number of subcutaneous formulations. Here ease of administration becomes critical.

Factors such as the ability to reduce administration frequency and provide less painful and quicker injections are also important considerations. Drug delivery devices need to be intuitive to use and should require as few steps as possible for administration; auto-injectors for subcutaneous injection that are automatic, and pressure activated rather than requiring buttons, can help severely ill patients manage their own medication at home without assistance.

Speed to market is also an important commercial consideration in drug development which may affect choices around both administration route and delivery device, while managing risk is a critical challenge throughout development: working with novel excipients and custom devices, for example, adds complexity and additional stability and safety studies may be needed. This increase in requirements may delay time to market but is critical

to provide assurance that the best drug candidate is taken forward and most appropriate delivery device is selected.

Propelled by these key drivers, formulation science is seeing some major key trends. These are:

1. The quest for biologic stability

Developing novel biologic formulations is fraught with challenges relating to stability, interactions with excipients, the primary container, oxygen and light sensitivity, high extrusion or shear forces. Novel excipients are being introduced to help with biologic stability and to also allow injection via the subcutaneous route. These may in turn permit the administration of larger volumes (>2mL), therefore reducing frequency of delivery. As a result, delivery devices must accommodate larger volumes in bigger syringe sizes: typically, 2.25mL. Having a platform device that can easily accommodate both 1mL and 2.25mL pre-filled syringes and a variety of fill volumes is a distinct advantage and allows flexibility throughout development and commercialisation.

An excipient which solves one issue, for example viscosity or stability, may, however, cause another, for example interaction with silicon in the glass primary containers. Innovation in this area has seen a lot of recent development, from novel glass coatings to enhance stability to the use of innovative plastic primary containers which aim to minimise protein aggregation in biologics caused by silicon.

The shelf life of a drug is typically around 2–3 years so being able to extend this with stability studies post-launch can provide a significant commercial advantage. Alternatively, storage at below room temperature is an option to extend shelf life but this route relies on patients remembering to keep their drug refrigerated and to remove it before use in the case of biologics, where low temperatures increase viscosity making the injection potentially more painful. In addition, there are implications in the supply chain where cold chain conditions may be required for these products.

2. Reduced injection frequency

There is a lot of focus on reducing injection frequency to provide increased patient convenience and therefore improve therapy adherence. Novel drug device combination products, including long-acting and extended-release formulations, help drive this. Increasing drug viscosity can also play a part in reducing injection frequency but here there are trade-offs for administration: needle length and gauge as well as potential impacts on pain on injection, increased injection or device hold time that may be inconvenient or even impossible for the patient to manage. In addition to this, there is the constraint posed by suitability and compatibility of the selected drug delivery device.

Increased focus on the patient experience, especially for those who self-administer, earlier in the drug development process does help to provide a more patient-centric approach. This can provide benefits ranging from reassurance to comfort, to convenience and is also seeing an acceleration driven by regulatory pressure to improve device usability.

3. Shift to larger volumes

In recent years, there has been a move from 1mL up to 2mL, and some exploration of 3mL-plus injectate volume for sub-cutaneous delivery to reduce injection frequency. It is likely that Injectate volumes for sub-cutaneous delivery will continue to increase from 2mL towards 3mL and beyond enabled by the introduction of novel excipients and additives to allow reduced pain on injection. Autoinjectors which have a two phased independent needle insertion and dose delivery can provide an improved and more consistent patient experience during the administration process even for volumes up to 2mL.

4. Diversified drug delivery

In addition to a growing range of formulations there are also increasing options available for subcutaneous delivery devices that range from safety devices for pre-filled syringes to disposable and reusable autoinjectors and also wearables. Each of these now has the capability to add connectivity, enabling transfer of key



patient data and the ability to measure and monitor therapy compliance.

Having more choice in delivery device allows the formulation experts to explore a variety of options: these might be formulation changes in early clinical studies, or the creation of a range of differentiated products which provide tangible patient benefits. With patients growing increasingly informed about their disease and treatment options, these options also provide them with choice around how they wish to manage their condition. In addition, choice of delivery method and device can also help to provide patient confidence and reassurance and may impact compliance to their therapy regimen.

There has been much focus and discussion on wearables as they could provide a more convenient and comfortable means to deliver therapies to the patient. However, with the exception of diabetes these have not yet become mainstream and there are challenges within formulation development, especially for biologics, that need to be addressed before this technology really becomes established.

5. Increased functionality Vs ease of use

With the rise of patient self-administration, the emergence of connected devices has started to play an increasingly important role in the communication and delivery of therapy, specifically in the role of devices in helping to drive improved patient therapy adherence through better support and HCP monitoring. In parallel, there has been a trend towards more complex devices with additional injection speed and depth features. Although these have been welcomed with enthusiasm, there is also the understanding that complex, connected

devices with numerous features and user steps may not be suitable for all patients and may present unnecessary cost. Devices need to be simple and intuitive in order to both minimise user errors and encourage adherence.

It's likely that in the future we may see a move to more streamlined, simpler devices which focus on the functionality that is really needed for effective drug delivery, such as efficient end-of-dose indicators, and avoiding over-engineered or complex features which can be either confusing, or not necessary for safe and effective use.

6. The drive for increased sustainability

Sustainability, including environmental awareness is also moving up the agenda in the pharmaceutical industry due in part to increasing pressure from governments, regulators, patients and consumers. This is now starting to drive change in multiple areas, from corporate operations to packaging and device choice and may lead eventually to formulation. Despite talk about green chemistry, the drive for improved efficacy is still the top priority for the formulation teams now increasingly coupled with a focus on risk mitigation relating to manufacturing and waste products.

From a drug delivery perspective creating formulations that allow a less frequent dosing schedule also means a reduction in number of disposable delivery device used over time. This has been possible, in part, by the development of higher viscosity formulations however these in turn create their own challenges with respect to patient administration and manufacturing. Viscosity can change over time and with temperature, influencing both injection time and the ability of the device to deliver the

dose effectively, making this an important consideration for device choice.

Finally, there are a number of trends currently impacting formulation and therefore drug delivery device design. From sustainability to speed to market, from usability to increased therapy adherence, all these drivers have a key feature in common: providing effective patient outcomes without knock-on effects in terms of cost or user experience. Understanding how the different demands can work in synergy will help shape the future of drug delivery.

REFERENCES

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