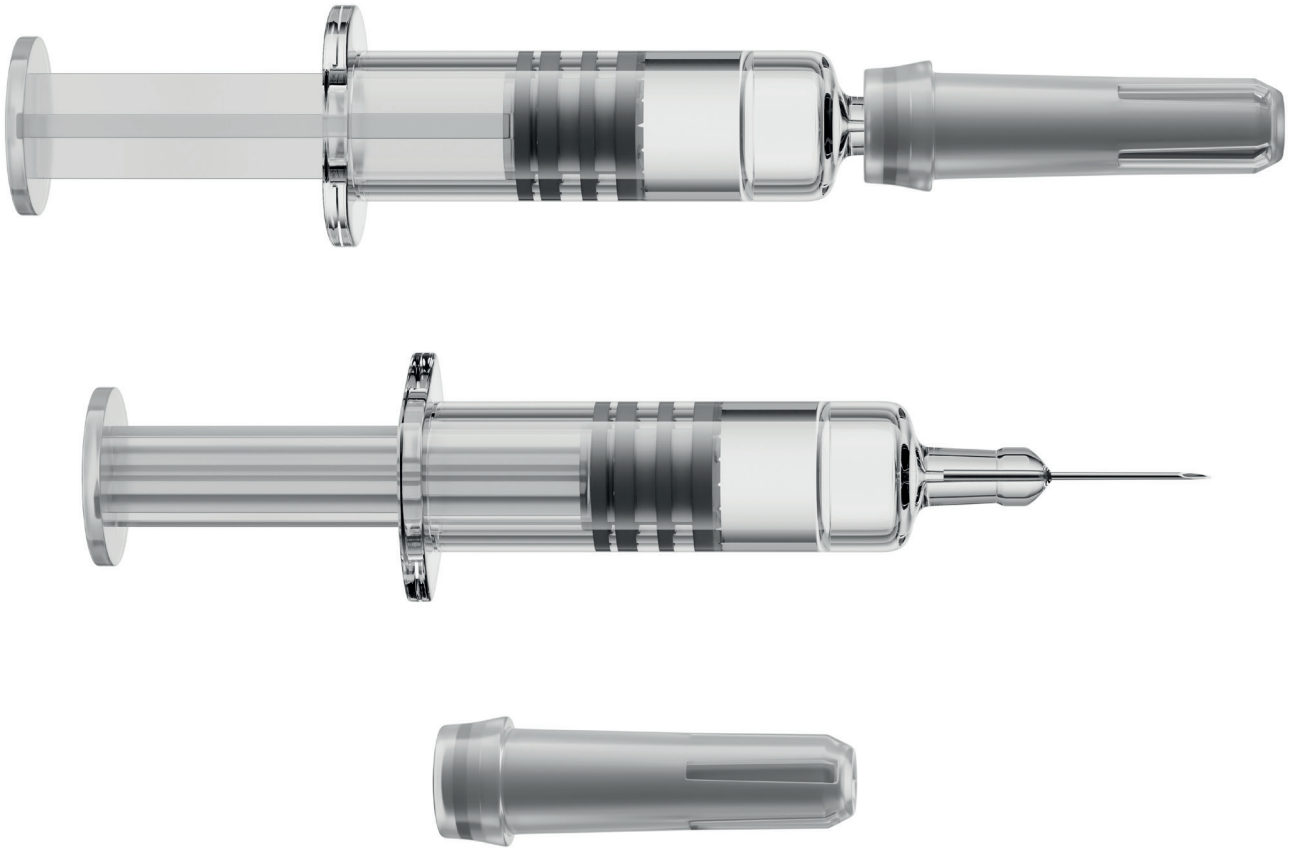
PREFILLED SYRINGES & INJECTION DEVICES

ON drugDELIVERY



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ANTICIPATING AND MITIGATING CHALLENGES IN THE COMMERCIALISATION OF PREFILLED SYRINGES & INJECTION DEVICES – A TECHNICAL DRUG PRODUCT PERSPECTIVE

Here Andrea Allmendinger, PhD, Chief Scientific Officer, and Hanns-Christian Mahler, PhD, Chief Enablement Officer, both at ten23 health, provide an insight into the challenges of integrated development of drug product and device design and fill-finish manufacturing operations.

Ready-to-use (RTU) delivery devices such as prefilled syringes (PFSs), autoinjectors, pens and large-volume injection devices are designed to facilitate administration for the end-user. This allows for self-administration, for example, in case of subcutaneously (SC) administered products, or increases patient safety, for example, for intravitreal (IVT) products administered by a healthcare professional.

The commercialisation of a combination product, such as a PFS or cartridge-based on-body injector (OBI), presents several key challenges during the technical development and manufacturing of the drug and drug/device combination product. This article provides a broad overview of most important challenges from a technical perspective and highlights the importance of integrated development of drug product and device design and fill-finish manufacturing operations.

PRODUCT CONFIGURATION

The selection of a suitable formulation for the API is essential to stabilise the product at the intended storage temperature over the desired shelf life. In particular, selection of the final dose, and therefore

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concentration of the API, is key as it defines the fill volume of the final drug product. For ophthalmologic products applied to the vitreous humour, the maximum injection volume is currently believed to be 100 µL. For SC administered products, injection volumes have been traditionally considered as limited to volumes of 1 mL or less.

However, knowledge and experience in the clinical setting is increasing with regard to tolerability and usability, and SC administration has recently been facilitated by the development of highly concentrated formulations of greater than 50 mg/mL at injection volumes up to 1, 2 or sometimes 3 mL. The question of what the limit is for SC volumes remains open, but it is inspired by the recent commercialisation of 10 mL cartridge-based OBI device of FUROSCIX (furosemide – scPharmaceuticals, MA, US).

Besides molecular/biochemical product stability, one of the main technical challenges of highly concentrated formulations is the exponential increase in viscosity with increasing protein concentration. Notably, viscosity is dependent on temperature and shear rate, and subtle variations of protein concentration, even within specifications, can lead to drastic changes in viscosity. Viscosity is associated with both challenges during filling, but also an increase in the injection forces required to administer the product. The latter needs to be mitigated by device design to guarantee functionality and adequate injection time upon stress, stability and transport testing to maintain patient usability.

The variability of components also plays a major role in potential product liabilities and risks. For example, the variability of the inner diameter of the needle used for injection impacts injection forces significantly (by the power of 4, according to Hagen-Poiseuille's law).

PRIMARY PACKAGING CONTAINERS – RTU CONFIGURATIONS

Combination products are typically filled in RTU primary packaging containers, such as syringes or cartridges, preferably in nest/tub configurations. This means that the container is provided in prewashed and pre-sterilised configuration and ready for filling. However, this implies that device attributes must comply with final drug product requirements throughout the supply chain until the point of filling. This includes the performance of the device and safety relevant parameters, including the risk of potential contaminants, such as absence of micro-organisms (maintenance of sterility) or particles. In particular, novel containers, an increasing number of which have been entering the market lately, require a thorough and, sophisticated characterisation of the primary packaging container and product compatibility. Specifications of primary packaging material must be carefully designed and assessed with the final drug product quality requirements in mind.

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However, "traditional" glass containers, such as glass syringes, also require a thorough characterisation of material attributes impacting the injectability over the intended final product-use time and contaminants, such as particle load, must still be assessed (and minimised). In essence, the characterisation of the primary components, with the end quality in mind, is key.

Testing the primary packaging material's compatibility with the drug product solution and its stability is essential, even more so if novel containers are used. Characterisation should include extractables and leachables testing, container closure integrity and product quality including, for example, particle contamination. Stability testing of drug product filled into the primary containers includes a panel of biochemical and pharmacopeial endpoints that cover critical quality attributes (CQAs), including content and purity, and obligatory CQAs, such as (sub-visible and visible) particulates.

FILL-FINISH PROCESSES

The drug product manufacturing capabilities must be aligned with the requirements of the device partner and primary packaging supplier to ensure that the drug product will adhere to agreed parameters. The drug product manufacturer needs to be capable of reliably and consistently filling the related primary packaging containers (e.g. larger-volume cartridges, syringes or special containers), ideally offering RTU containers.

The filling process is especially challenging for highly viscous and low-volume products. The manufacturer should be able to handle a highly viscous product from the processing side, such as by choosing between different pumps, and be able to choose between weight or volume fill.

In general, overfills must be minimised as this is likely to result in significant cost savings. This is especially important for IVT products. Administration volumes of IVT products are in the range of 10–100 µL, which is often much less than the minimal volume that can be filled by most sterile facilities and contract manufacturing organisations. As a result, most products for IVT use are significantly overfilled. In addition, this also means that syringes for IVT use need to be manipulated by the final user, preferably a healthcare professional, by either expelling air or volume, which is also referred to as "downdosing". However, this carries a risk of variability in the volume administered.

Another challenge arises during (air) transport. The design of fill volume and allowable headspace with the chosen primary packaging is key as the transport conditions may lead to stopper movement, which may impact container integrity and, hence, potential loss of sterility. Therefore, a bubble-free plunger setting at the manufacturer facility allowing for minimal headspace, as well as the control of the plunger stopper position and stoppering under vacuum to allow reduced plunger compression (for example, for silicone-free container closure systems) is beneficial.

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CONCLUSION

Joint and integrated development between product development – including formulation design – and selection of primary packaging container, device design and manufacturer is essential to transfer product knowledge, facilitate troubleshooting activities and enable successful commercialisation. Challenges and failure modes need to be appropriately assessed *a priori*, and appropriately mitigated and managed. This includes appropriate formulation development, manufacturing process design and holistic consideration of the interplay of the formulation and raw materials, primary packaging, fill process unit operations, usability and administration, as well as all their acceptance criteria and specifications, in order to yield a safe and efficacious final product.

ABOUT THE COMPANY

As a CDMO, ten23 health is appropriately positioned to anticipate and overcome the challenges that relate to sterile drug products, especially for SC or IVT use. The company offers integrated development of formulation services, analytical development and product characterisation, device selection and testing, drug product process design, product characterisation and failure mode assessments with its high-end capabilities in particulate characterisation and injection force and container closure integrity testing. ten23 health also provides fill and finish (sterile manufacturing) of complex and high-precision containers at its facility in Visp, Switzerland, including syringes, vials and cartridges, for both glass and novel containers (Figure 1).

Figure 1: ten23 health's facility in Visp, Switzerland.

ABOUT THE AUTHORS

Andrea Allmendinger, PhD, has been Chief Scientific Officer at ten23 health since November 2021. Dr Allmendinger is also Adjunct Professor and Group Leader at the University of Freiburg (Baden-Württemberg, Germany), researching novel parenteral drug formulations and device solutions to improve stability, usability and cost of goods. Between 2010 and 2021, she was Principal Scientist, Pharmaceutical Development at Roche, working on, *inter alia*, manufacturability and injectability of high-concentration formulations, syringe and high-volume drug/device combination products, particulates and surfactant strategy. Dr Allmendinger studied Pharmacy at the University of Heidelberg, Germany, and University College London, UK, and holds a PhD in Pharmaceutical Sciences from the University of Basel, Switzerland. She obtained the *venia legendi* (German Habilitation) from the University of Freiburg in 2021, and serves as Editor-In-Chief for the AAPS Open Journal.

Professor Hanns-Christian Mahler, PhD, is Chief Enablement Officer and Board Member at ten23 health. He previously led the Drug Product Services Business Unit at Lonza AG (2015–2021) and worked in various leadership roles, such as Head of Pharmaceutical Development & Supplies at Roche (2005–2015) and Merck KGaA (2000–2005). He has extensive expertise in formulation development, process development and validation, packaging/device development and integration, sterile manufacturing and regulatory submissions with numerous IND/IMPD and BLAs. Prof Mahler studied pharmacy at the University of Mainz, Germany, and holds a PhD in toxicology from the Institute of Pharmacy, University of Mainz, and pharmacist specialisation degrees in toxicology and ecology, and pharmaceutical technology. He also has qualifications in Business and Marketing (AKAD University, Germany). Prof Mahler obtained his *venia legendi* from the University of Frankfurt, Germany, in 2010 and is adjunct faculty member and lecturer at the universities of Frankfurt and Basel. He also serves as Editor for Pharmaceutical Research, Journal of Pharmaceutical Sciences, AAPS Open Journal and PDA Journal of Pharmaceutical Sciences and Technology.

ten23 health
Design. Formulate. Deliver.

Comprehensive pharmaceutical services for sterile dosage forms.

The complexity and diversity of modern therapeutics is increasing. Medical research is facing growing challenges of stability, usability, and consistent manufacturing.

Pharmaceutical products need to be designed with the patient and regulatory requirements in mind, in order to deliver safe, effective, high-quality, and easy-to-use medicines. At ten23 health, we integrate different elements such as formulation development, manufacturing process design, control strategy, primary packaging, and device selection, to achieve a holistic product design from the start.

- Formulation development for liquid and lyo
- Sterile drug product development for different modalities
- Sterile manufacturing under cGMP (vials, syringes, cartridges)
- Administration compatibility testing
- Syringe development, manufacturing, testing
- Primary packaging material characterisation

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