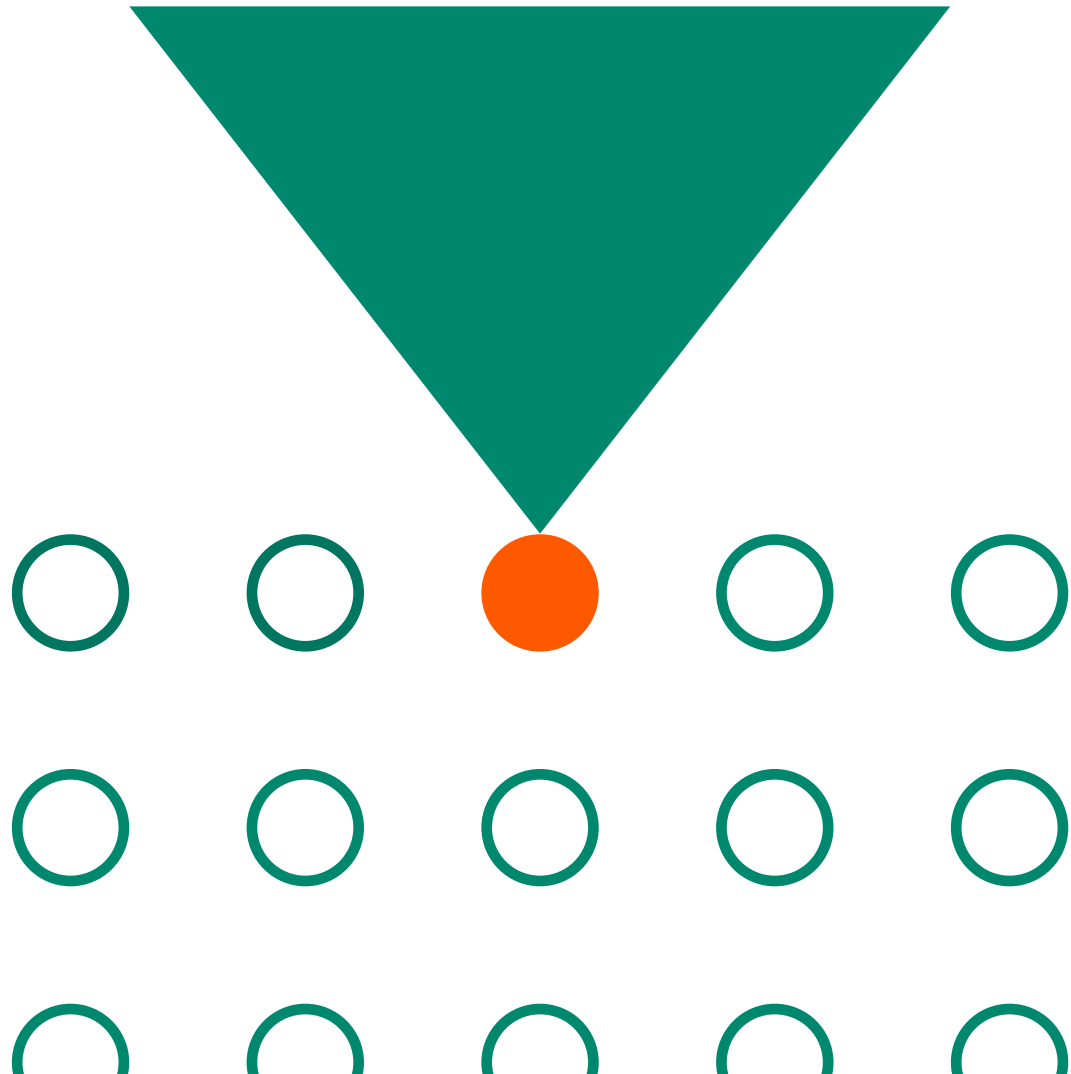
cytiva

Manufacturing challenges with high concentration biologics



Summary

Growth in the formulation of drugs suitable for delivery by subcutaneous (Sub-C) injection highlights manufacturing challenges associated with the higher concentration of active ingredients and formulation components. Manufacturing unit operations that are directly impacted by higher concentration formulations range from ultrafiltration to sterile filtration, filling, mixing and storage. Good solutions need to maintain quality, maximize process yield and product recovery and would benefit from being adaptable to existing manufacturing platforms. This white paper takes a look at key process operations, outlines some of the challenges faced when manufacturing high concentration biologics and provides factors to consider when optimizing process.

Introduction

The specificity, and at the same time, versatility, of monoclonal antibody (mAb) therapies continues to make them a strong candidate for the treatment of a wide variety of diseases, including autoimmune and cancer therapies. As the list of diseases that can be targeted by mAbs, recombinant proteins (rPro) and antibody-drug conjugates (ADC) grows, opportunity arises to address challenges with the method of administration, thereby improving the experience of the patient and easing the burden of the healthcare provider.

The last decade has seen the most rapid advances in the enablement of subcutaneous delivery methods as opposed to intravenous (IV) infusion. Research data, as displayed in Figure 1, confirms the increasing prevalence of sub-cutaneous administration as drugs progress to approval[1]. Subcutaneous delivery provides the option for self-administration of the therapeutic by the patient. This reduces frequency and duration of any visit to the clinic, improving both the patient experience, and significantly lowering healthcare costs associated with the longer, more complex IV infusion.

Producing a drug product that can be administered in this way requires careful formulation to deliver the desired dose in a volume that can be tolerated and absorbed. Therapies for administration via IV are typically in the order of 20 to 50 mg/mL with a total dose around 300 mg. The same dose when administered via subcutaneous injection requires lower volumes, typically 1.5 to 2 mL. This, in turn, requires higher concentrations in the range of 100 to 200 mg/mL. The first monoclonal antibody for subcutaneous delivery was approved in 2003 and since then of the 103 monoclonal antibodies approved, 26 of them are high concentration monoclonal antibodies[2]. A recent survey allowed us to gather data on more than 100 molecules in development across 20 companies, highlighting that almost half of these drug products had a final concentration greater than 100 g/L (see Fig 2).

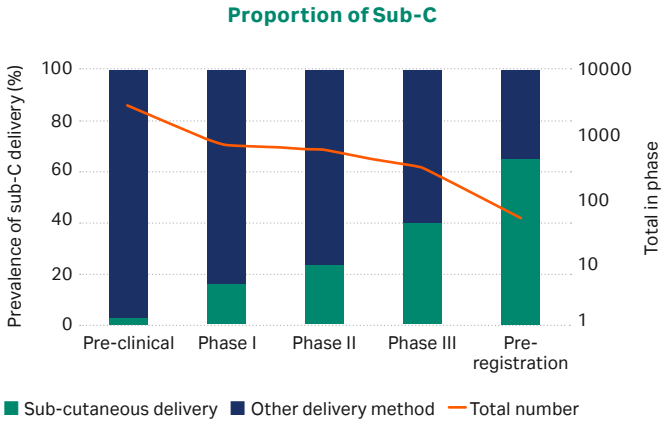


Fig 1. Biological drugs in development with a described route of administration ref: GlobalData.

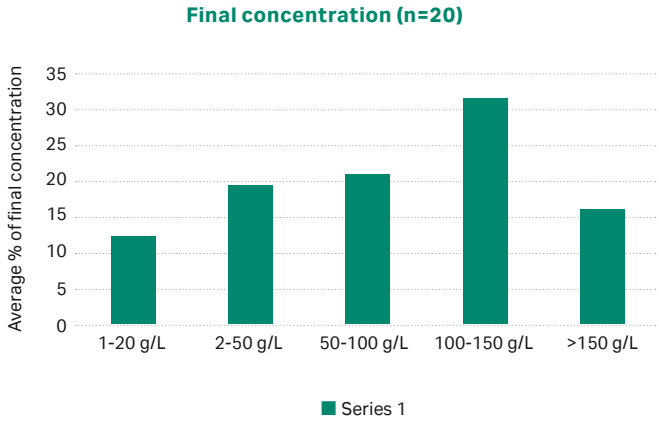


Fig 2. Survey of Cytiva customers developing biological drugs.

High concentration — a production challenge

In 2018, the Subcutaneous Drug Delivery and Development Consortium was convened to identify and address key issues and gaps concerning patient pain points, formulation, and manufacturing challenges with respect to production and delivery[3]. Amongst the problem statements addressed were those on viscosity, aggregation, and instability, and the effect of excipients on formulation, filtration, fill and finish and bioavailability. Similar challenges are reported in other literature and different formulation strategies can be the pathway to overcome them[4].

The effects of excipients in formulations

While development of the active pharmaceutical ingredient (API) occupies much of the average development timeline, optimization of the formulation to assure bioavailability of the drug is critical to the success of the final product. Although formulation optimization requires close attention, it is a common practice to accelerate development utilizing existing formulation platforms and adapt them to carry different APIs.

A typical biologic drug formulation consists of the active ingredient such as an antibody or recombinant protein, and inactive formulation ingredients or excipients which include buffers, surfactants such as polysorbate 20 and polysorbate 80, and amino acid salts such as arginine and sugars. The ratio and quantity of inactive excipients need to be optimized to ensure product stability and inhibit aggregation at higher concentrations by weakening the protein-protein interactions. Excipients can be used to control viscosity and provide protection against shear stress. They can also minimize surface absorption.

Additional formulation ingredients such as enzymes enhance absorption and bioavailability[5]. These include hyaluronidase which opens the inter-cellular matrix, by degrading hyaluronan which acts as a barrier to absorption. Such additions allow for greater subcutaneous injection volumes and supports improved and faster dispersal of the therapeutic, improving the bioavailability of the monoclonal antibody.

The effect of high concentrations on process operations

The mix of antibody concentration and excipients can impact the process operations imported from lower concentration manufacturing platforms. These may affect performance of the specified technology, add additional quality risks, or reduce yields. The increasing value of the drug makes any losses highly undesirable and re-optimization of an existing platform technology or adopting alternative approaches to the same operation are worthwhile consideration, both to overcome quality risk and loss in yield. The utilization of existing platforms is clearly a win for both cost and time effectiveness but finding and optimizing a unique formulation may result in a more stable, less viscous product. Reformulation is a slower process and there is a risk that the final drug may not meet its intended shelf-life, especially where there is a need to balance multiple competing degradation pathways[6].

Process operations typically affected by an increase in biologic concentration and viscosity are:

- Ultrafiltration / diafiltration
- Sterile filtration
- Bulk filling, storage, and transportation
- Mixing
- Final fill and finish

Ultrafiltration / diafiltration

Product concentration and buffer exchange into the desired formulation conditions is the first stage where the preparation of a high concentration drug substance begins. To prepare lower concentration feed it is usual to employ flat-sheet cassettes and a product recirculation to slowly increase the concentration towards the target. While this typically may be a 3-to-5-fold concentration for traditional formulations, a requirement to deliver a concentration greater than 100 g/L extends this process to achieve a 10 to 20 fold concentration. As retentate viscosity increases, the differential and transmembrane pressures increase significantly demanding careful control.

The combination of extended recirculation, and the increasing concentration carries a significant risk of shear-related damage that may impact product quality. This, coupled with the increased protein interactions from the rising concentration, may lead to higher levels of aggregation. This reduces quality further, lessens yield or fouls the ultrafiltration membrane to further extend the process time or jeopardize the successful completion of the process. In addition, product recovery techniques that involve over-concentration and buffer flushing may not always be practical with higher target concentrations.

The likelihood of aggregation may be reduced by diafiltration into a stabilising buffer while still relatively dilute, however this increases the volume of buffer required, extends the process time and continues to expose the product to shear forces associated with recirculation. Single-pass tangential flow filtration (SPTFF) may offer real benefits over the recirculation alternatives. This may be in the form of pre-concentration using simple in-line concentration and in-line diafiltration devices, or through fully controllable SPTFF systems capable of accurately controlling the concentration factor. However, the lower hold-up volume of an SPTFF system, when compared to a conventional TFF system, allows for enhanced product recovery and a higher step yield at higher concentration. Real-time protein concentration monitoring may also support the characterization of these processes and alleviate the need for sampling and off-line analytical testing.

Sterile filtration

Filtration, post-concentration and post-formulation, controls process bioburden and, in the context of bulk filling and filtration before final filling, is critical to the quality and safety of the drug product. The additional challenges presented to the filter as a result of higher concentration and formulation components must be well characterized.

Critical filtration processes need to be fully validated to ensure the filter can achieve the desired level of bacterial retention in accordance with the guidelines laid out by the relevant regulatory authority. In most processes, this is a formality however, for process fluids with known risk factors it is important to ensure that the selection of the filter is driven with a full assessment of process risk[7]. Risk factors include higher viscosity and the presence of surfactants, typical to high concentration biologic formulations for subcutaneous injection. When retention performance of the filter options appears equal, performance in terms of throughput can have a real impact upon the process. Smaller filters, enabled by high throughput characteristics, intrinsically lead to lower non-recoverable fluid losses than larger filters. Selection of filters and system designs that accept fluid losses as being unavoidable, are a compromise that result in loss of highly valuable product. At the point of bulk fill for example, a recent survey we conducted with manufacturers of high concentration biologics discovered that these combined losses could be as high as $50K per batch. This is a major consideration when designing the process. The filter choice for high concentration biologics is effectively characterizing membranes that are designed to perform well with viscous fluids but have a lower effective filtration area (EFA).

Beyond yield, the additional formulation components that are critical to product stability may also provide some filtration challenges. Typical excipients such as polysorbate 80 can easily be adsorbed by some materials used in filtration media and reduce transmission. Vendor data that characterizes this aspect of filter performance within its validation package will clearly be advantageous when choosing a filter.

Bulk filling, storage, and transportation

While these processes are largely identical to those from a lower concentration process, the lower volume and higher drug value per milliliter amplify any product losses. The risk of product loss during storage and transportation is also brought into sharper focus than normal as the relative impact of loss associated with any bioprocess container failure increases.

It is not uncommon for bulk drug substance to be frozen. This is one way to build flexibility into the process and to ‘stop the clock’ on any degradation pathways that may impact shelf life and product quality. Solutions that protect frozen biocontainer bags during storage and transportation to the filling location are desirable and again this is amplified by the higher value product.

One potential issue with this approach is the control of both the freezing and thawing processes to safeguard and standardize product quality. The higher concentration potentially increases the risk of aggregation associated with freeze concentration and the highest degree of control is needed to guard against small variations in the freezing kinetics from having a significant impact on the critical quality attributes. Plate freezing systems using 2D biocontainer bags, apply a higher level of control than 3D bottles due to the faster freezing and close temperature control that remains consistent, regardless of batch volume. This is not achieved with traditional blast freezing where the freezing kinetics will vary between large volume batches and the smaller batch volume of higher concentration formulations.

Mixing

Maintaining product homogeneity in a more viscous fluid can require mixing systems that can provide the necessary power without the shear that may damage the biologically active ingredient. Systems with impellers designed for high power input but low shear for relatively small volumes at high concentrations are required to safeguard against product quality issues.

Stress induced by mixing is a reality and with biological compounds being more sensitive in nature, thoughtful process design in this area is worth the time invested to get it right. Careful consideration for how both integrity and functionality of a product can be maintained during mixing, without contamination or degradation occurring, is a must[8].

Optimal blade design when mixing highly viscous biologics could make a significant difference with product yield. Powerful mixers need the ability to efficiently transfer torque into a fluid at reduced speeds. Combine this with levitation technology, based on non-contact magnetic coupling, can create an ideal mixing environment for sensitive applications.

Final filling

Fill and finish, the final operation in the drug product manufacturing process can also lead to problems and product loss without adequate consideration. The higher protein concentration and higher viscosity mean that filling needles could be prone to dripping and may increase clogging from crystalized protein at the needle tip. This leads to inaccurate dosing, or even interruption of the filling run, both risking significant losses of high value product. Filling needles that are manufactured from hydrophobic materials such as reinforced polyether ether ketone (PEEK) can reduce drip formation. Optimizing filling needle size and your filling flow regime can also guard against drips and clogging and safeguard valuable product at a critical point in the process.

Conclusion

High concentration biologics and the increasing demand to provide drugs via sub-cutaneous delivery as a way of administration, is a path that the biotechnology and gene therapy industry has been travelling for some time. It brings with it challenges that have the potential to be both costly and time consuming. However, robust process operations inclusive of high performing filters that have a lower EFA to reduce hold up volumes and adsorption losses, and optimized mixing, purification, and final fill and finish steps, go a long way to meet the new challenges faced.

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