BIOTECH

White Paper

USD 3779

# High Concentration Monoclonal Antibody Drugs

## Manufacturing Challenges

# Contents

## 1 Summary

The 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 required. Manufacturing unit operations that are directly impacted by higher concentration formulations range from ultrafiltration to sterile filtration, filling, mixing and storage. Solutions that maintain quality, maximize process yield and product recovery are available and can be introduced to adapt an existing manufacturing platform to the new process requirements.

## 2 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 mAb and recombinant proteins (rPro) grows, their relative maturity permits opportunities 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 the routine intravenous (IV) infusion. Subcutaneous delivery provides the option of self-administration of the therapeutic by the patient, reducing frequency and duration of any visit to the clinic, improving both the patient experience, and reducing healthcare costs associated with the longer, more complex IV infusion. Data in GlobalData (Figure 1)[1] indicates an increasing prevalence of subcutaneous administration as drugs progress to approval.

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 20-50 mg/mL with a total dose around 300 mg. The same dose when administered via subcutaneous injection requires lower volumes, typically 1.5-2 mL. This, in turn, requires higher concentrations in the range of 100-200 mg/mL. The first monoclonal antibody for subcutaneous delivery was approved in 2003 and since then of the 103 monoclonal antibodies approved, 26[2] of them are high concentration monoclonal antibodies. Data gathered in a recent survey by Pall Corporation of more than 100 molecules in development across 20 customers (Figure 2), highlights a significant proportion of drug products will present with a final concentration in this range.

**Figure 1**

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

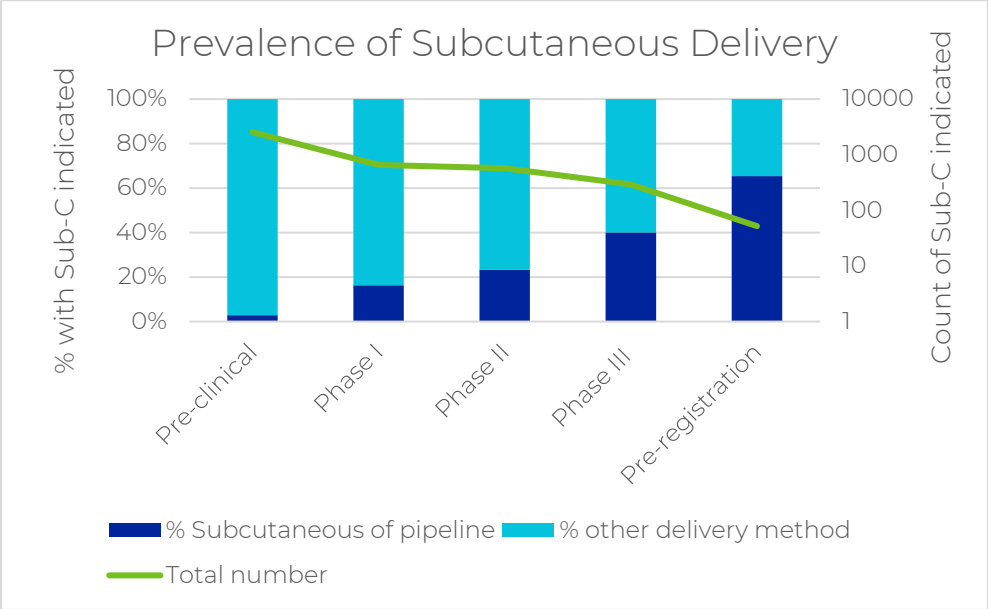
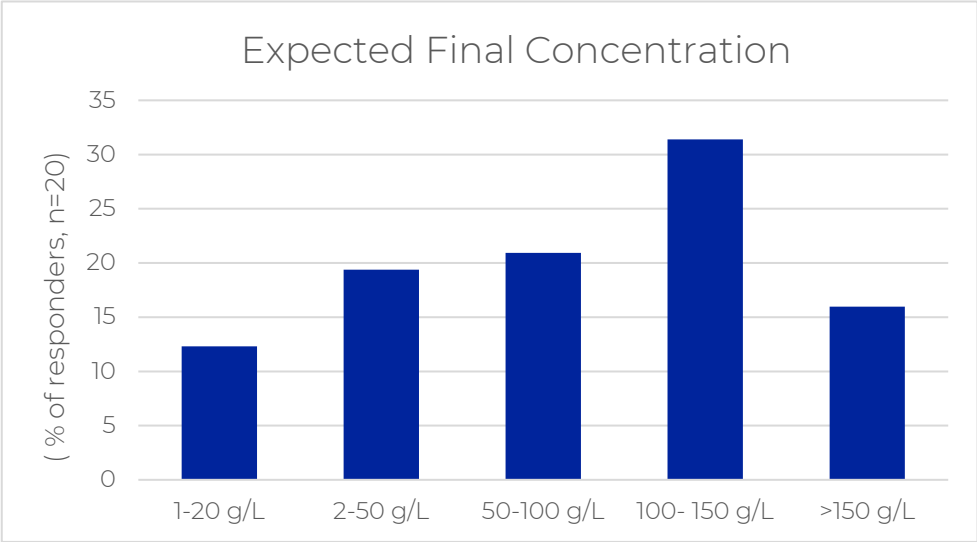


**Figure 2**

Survey of Pall customers developing mAbs and rPros




## 3 Concentrating on the 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, and fill and finish and bioavailability. Similar challenges are reported in other literature[4].

### 3.1 Formulation

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 necessary. This requires additional attention, although it is common for formulation platforms to be adapted to carry different APIs to accelerate development in the same way as manufacturing platforms achieve the same.

A typical antibody formulation consists of the active ingredient (the antibody or recombinant protein) and inactive formulation ingredients or excipients. Formulation ingredients include buffers, surfactants such as, polysorbate 20 and polysorbate 80 and amino acid salts such as arginine and sugars. These are optimized to ensure stability and inhibit aggregation at the higher concentrations by weakening the protein-protein interactions. These may also control viscosity and provide protection against shear stress. Ingredients can also minimize surface absorption.

Additional formulation ingredients such as enzymes enhance absorption[5] and bioavailability. 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 better and quicker dispersal of the therapeutic improving the bioavailability of the monoclonal antibody.

# 4 Typical 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 hence re-optimization of an existing platform technology or adopting alternative approaches to the same operation are worthwhile, both to overcome quality risk and loss in yield.

## 4.1 Ultrafiltration/Diafiltration

Product concentration and buffer exchange into the desired formulation conditions is the first stage where the preparation of the 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. Even with this control, there are challenges.

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, reduces 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, making over-concentration an additional challenge.

The likelihood of aggregation may be reduced by diafiltration into a stabilizing 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. Moreover, the lower hold-up volume of a 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.

## 4.2 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[6] it is important to ensure that the selection of the filter is driven with a full assessment of process risk. Risk factors include viscosity and surfactants, both present in 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 required because of relatively low throughput. This is furthered when the chosen filter is installed in a system that is designed to minimize non-recoverable volumes. Sub-optimal filter selection and system designs that accept fluid losses as being unavoidable lead to the loss of highly valuable product. At the point of bulk fill for example, a recent survey by Pall Corporation discovered that these combined losses could be as high as $50K per batch. This is worth considering when designing the process.

Beyond yield, the additional formulation components that are critical to product stability may also provide some filtration challenges. Components such as polysorbate 80 can easily be adsorbed by some materials used in

filtration media. Vendor data that characterizes this aspect of filter performance informs a filter selection that minimizes these losses.

### 4.3 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 mL 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 as 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 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 blast freezing where the freezing kinetics will vary between large volume batches and the smaller batch volume of higher concentration formulations.

### 4.4 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 biological 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.

### 4.5 Final Filling

The final operation in the drug product manufacturing process can also lead to problems and losses without adequate consideration. The higher protein concentration and higher viscosity mean that needles with internal bores are not optimal and materials that are prone to dripping 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.

Needle choices with materials that reduce drip formation, coupled with optimal bores and filling flow regimes guard against filling issues and safeguard valuable product at a critical point in the process.

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