For further information please get in touch with us

Vetter Pharma International GmbH
Eywiesenstrasse 5
88212 Ravensburg
Germany

phone: +49-(0)751-3700-0
fax: +49-(0)751-3700-4000
e-mail: info@vetter-pharma.com

Vetter Pharma International USA Inc.
4901 Searle Parkway, Suite 300A
Skokie, IL 60077
USA

phone: +1-847-581-6888
fax: +1-847-581-6880
e-mail: infoUS@vetter-pharma.com

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Anticipating success: Meeting the inherent challenges of complex drug substances

Introduction

Realizing the full potential of a novel injectable drug compound is no small task. In the months and years that lead from the exciting discovery phase to the rigorous demands of a commercial launch, unexpected scientific and technical challenges can slow development to a halt, often at key stages.

A careful, systematic approach to identifying where and why these roadblocks can occur is fundamental to staying on course. Just as important is a robust, repeatable process design focused on retaining the stability of a compound as it moves through clinical development. The early-stage data captured during this period can play a valuable role in an efficient transition from lab to clinic to market.

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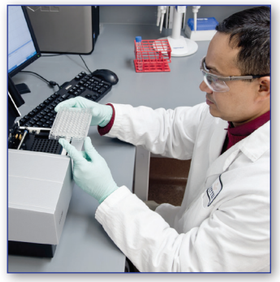
New directions in medicine/market trends



The last decade has seen remarkable breakthroughs in injectable drug therapies. Not surprisingly, the factors behind their development are as complex as the diseases and conditions to treat. Shifts in global populations have changed the pattern and spread of many infectious diseases, dictating more responsive approaches to the production of vaccines and other drugs. Intensive research into treatments for chronic disease states has ushered in a new generation of biotech compounds, many with highly sensitive or time-controlled delivery requirements.

Just as importantly, trends in patient care and drug safety have increased the demand for delivery systems that allow patients to administer their own injectable medications with fewer steps and reduced risk of dosing errors.

On the economic side of the equation, even small amounts of fragile biotech compounds can be extremely costly. Great care must be taken to optimize yields during development as well as reduce waste during manufacturing. Technologies that reduce overfill of high-cost molecules and provide greater dosing precision play an increasingly important role in realizing both the therapeutic and financial potential of novel drug products.

Yet another driver in the evolving biotech market is life cycle management. As patents expire or mature products are suddenly faced with new competition, innovative delivery formats that add value and convenience in the clinical environment can often be used to prolong a branded drug's premium pricing and define its market share against competitive entrants with similar indications and patient profiles.

Vetter is a global leader in aseptic filling and finishing, with a foundation of experience spanning more than 25 years and dozens of successful pharmaceutical and biotech compounds. We offer specialized resources from development and clinical supply to commercial fill and finish and life cycle management.

Identifying roadblocks to successful development

Monoclonal antibodies, multivalent vaccines, and recombinant peptides are all examples of complex products emerging from today's leading biotech and biopharmaceutical firms. As their complexity increases, so does their sensitivity to environmental conditions. A long list of inherent obstacles can ultimately affect both the time and costs involved in moving through clinical trial phases to commercial production.

From the start of the development process to create first-in-human-use material, companies need to focus their attention on the design of the filling process.

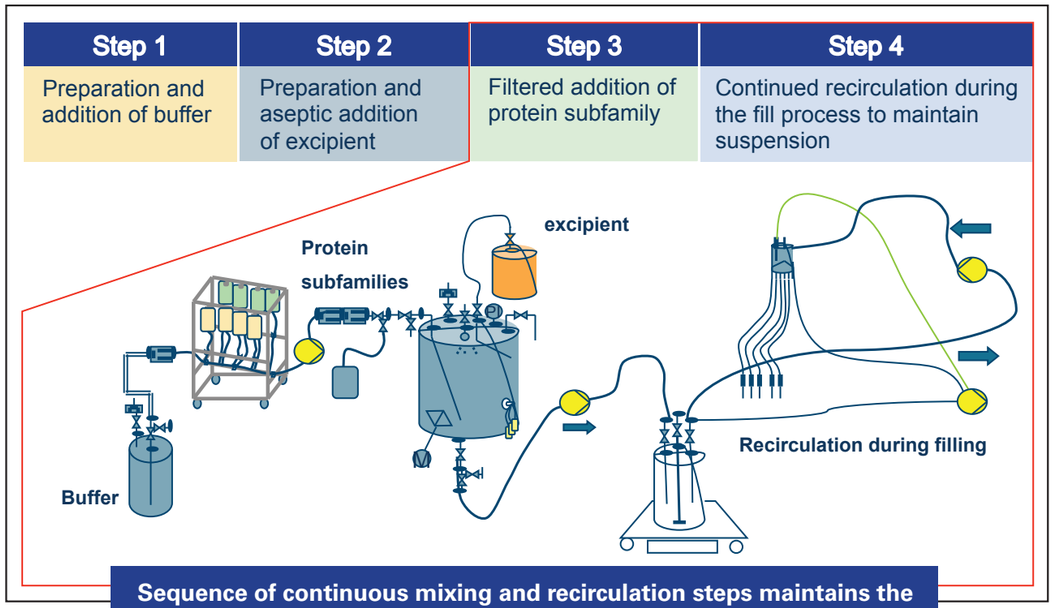
Some of the main questions that need concrete answers include:

- How robust is your compound to the process?
- How does the filtration process affect the biological potency?
- Is the drug product compatible with related components like rubber stoppers and closure systems?
- How much silicone can the substance endure? And how can it be applied?
- What materials are suited for the components, and do they have to be pretreated?
- How is your substance's susceptibility to interfaces?
- How is the substance's break-loose and glide force behaviour?
- How should sterilization be performed?

Practical solutions to meet the challenges of filling complex proteins

Potential incompatibility of complex proteins with various contact surfaces is a major concern, as is the possibility of leachable substances from the packaging material. In addition to protein stability, several other technical challenges faced by manufacturers including functionality issues (break-loose, glide force, and tip-cap removal force), filling issues such as plunger movement during shipping, and container closure integrity also need to be addressed.

The recirculation solution



Sequence of continuous mixing and recirculation steps maintains the biological potency of the vaccine all the way through final filling

An example of a four-step design processes for a multivalent vaccine with multiple protein subunits, aseptic filtration and recirculation during filling

Sterile process design for the filling of complex products

Highly sensitive biologics and conjugated peptides might be affected by filtration in the scale-up and filling process. There are many key variables to control, including fill concentration, viscosity, and pumping pressure.Multistep filtration processes might have to be developed to prevent protein aggregation during pooling and to eliminate leaching or any filter particles or extractable compounds in the final drug solution. Recirculation of the compounded drug substance may need to be included during the final filling step to maintain targeted concentration.

High viscosity during filling

To facilitate drug effectiveness and patient convenience, many biological-based drug manufacturers are looking to increase the concentration of their compounds in use. Higher dose applications of complex proteins bring a number of formulation challenges, mainly relating to the problem of protein aggregation and corresponding challenge of subvisible particles and protein stability. However, other technical aspects of process design in respect to high-concentration drugs need to be considered. The main issue is that the increased viscosity of the high-concentration product leads to accelerated drying on contact with surfaces during the filling process. One area that needs to be especially closely monitored are the filling needles. Highly viscose liquids can dry rapidly within the bore or at the needle between filling operations.

This has an impact on:
■ fill inaccuracy
■ misdirected fluid stream
■ contamination of other units with solid drops
■ difficulty with cleaning
Several corrective actions can be deployed to prevent problems in the process design:
■ Rinsing of fill needles at defined time periods in case of machine stoppage
■ Exchange of fill needles when exceeding the defined machine stoppage time
■ Use of larger needle (inner diameter)
■ Adjustment of pump parameters
■ Needle-tip design

Analytical expertise

Complex compounds by nature are a challenge to analyze correctly. Previously qualified methods formally need to be cGMP validated and then successfully reproduced routinely with a level of robustness to meet regulatory requirements. Expert teams work on reproducing previously designed methods, and seek solutions and possible alternatives. The spectrum of expertise needs to cover development and quality control analysis of the primary packaging material and compounding component materials associated with the starting API used in filling. These methods range from standard IPC testing to complex customer-specific methods for large protein characterization. Tests range from trace heavy-metal contamination, dissolved oxygen in the product or head space, subvisible particle characterization and release testing and stability testing. Different but comparable tests for the same compound may need to be implemented at different stages of manufacture, some of which will need to be planned as in-process and non-destructive. Once the compounding and filling process is developed, formal qualification batches need to be analyzed with a subset of methods required for formal release and stability testing.

Stability analysis

Stability tests are associated with the complete life cycle of a pharma product. This starts at formulation development as well as qualification and commercial batches through stability data for regulatory release of the clinical material. Late-stage reformulation or changes in packaging material or filling processes to provide proof of bioequivalence also require such analysis. There are also ongoing annual stability studies to correlate shelf life in the field once the drug is commercially launched to preempt possible supply shortages. Having the validated test on hand as the drug is manufactured is one aspect. The other is having enough ICH-conform, temperature and humidity controlled, and monitored stability space. The stability storage space needs to be requalified on a regular basis and have backup sytems in place to prevent changes to conditions if original power supplies are interrupted.

Vetter has a large multidisciplinary expert team with over 15 years of complex compound analytical method experience with a wide range of analytical devices. Method transfer for over 30 different products are carried out anually. Vetter has currently up to 370 m² in stability storage space. There are currently more than 65 products consisting of several batches included in stability programs at Vetter.

Storage condition	Storage room in total
25°C / 60% RH	136 m²
30°C / 65% RH	66 m²
40°C / 75% RH	57 m²
2° to 8°C / ambient RH	110 m²

Vetter stability storage space at a glance

Method transfers between labs

Each particular method transfer needs to be performed in compliance with cGMP requirements. This requires a level of systematic project management and formal documentation. Sometimes a covalidation needs to be carried out between labs, or the analytic method needs to be optimized and formally validated.

The final validated analytical method is only ever as good as the completeness of the qualification plan, training documentation, and qualification report for the regulatory authorities. Mistakes or poorly documented material can cause significant delays downstream during the submission process.

Summary

With years of experience in the development, manufacturing and analysis of injectable compounds, Vetter brings a unique blend of people, processes, and technologies to the special challenges of developing new and sophisticated drug products.

Our approach draws heavily on practical, experience-based solutions, implemented by core teams of experts trained to identify and solve complex, time-sensitive problems. Renowned specialists in disciplines such as siliconization, lyophilization, analytical methods and method transfers,stability testing and process optimization further support our rigorous and well-planned development process.

These teams work closely together and with our customers from initial studies through regulatory filing and manufacturing, focused on the goals of reducing time-to-clinic while achieving maximum yield from API. Along the way, we also integrate key steps with important long-term outcomes, such as careful collection of data during process design and testing.

Data gathered from these early-stage results not only incorporates critical parameters that streamline later scale-up steps, but also helps to avoid costly delays during initial regulatory submission. Continual investment in technologies, training, and processes plays a central role in our ability to deliver consistent, high-quality results. From state-of-the-art equipment and facilities to customized, integrated software for quality monitoring, we are constantly working to meet the highest possible performance standards to support our clients' unique drug products.