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Advances in Manufacturing and Processing Impacting Formulation Development

Achieving investigational new drug (IND) approval at an increasingly faster rate than competitor drugs is a widespread desire of biologics developers. This has been further amplified by the need for treatments and vaccines for the COVID-19 pandemic. As a result, the pressure to achieve speed in drug formulation development has escalated to new heights.

With research and development into new drug modalities and technological advances in manufacturing processes over the past decade, biologic drug formulation development requirements have evolved. These range from finding new formulation conditions for multiple new drug modalities to minimising the burden of treatment, easing patient administration, and ensuring device development for drug compatibility.

In this article, Heonchang Lim of Samsung Biologics, offers insight into the common hurdles that must be overcome in formulation development to meet these various requirements. Lim also explores the need for manufacturers to adopt strategies considering these challenges that will enable timelines to be reduced and essential drugs to be delivered to patients faster.

Tools to Assess Drug Formulation Feasibility

The formulation of biologic drugs, such as protein-based products like monoclonal antibodies (mAbs) is a difficult and time-consuming process, in part due to the often-complex protein structure. The success of most biologics is dependent on the active form being delivered to its site of action. To achieve this goal, there are many characteristics of the drug that must be considered, including pharmacokinetics, toxicity, clinical indication, and physico-chemical stability.

Prior to formulation development, verifying drug formulation feasibility will help developers to select an optimal candidate in terms of developability among several molecular candidates. Formulation feasibility studies can be conducted using various *in silico* and *in vitro* assessment tools.

In silico assessments rely on data on the molecule's amino acid sequence and structure and aim to minimise the risks in terms of the molecule's stability. For mAbs, this could include evaluating the liability of the molecule's complementarity-determining region (CDR) using its protein sequence.

If utilising deep learning technologies for the prediction of a protein's tertiary structure, *in silico* assessments can be used exclusively for feasibility studies. However, deep learning systems are at an early stage and may not be suitably effective for all analytical functions.

Therefore, *in silico* assessments will more commonly utilize SWISS-modelling-based structural predictions. These can be used to evaluate mAb formulation feasibility. However, the structure of proteins like bi-specific antibodies (BsAbs) or Fc fusion proteins, including the folding and other aspects of their tertiary structure are generally too complex for SWISS-modelling methods. Therefore, most developability evaluations are confirmed using *in vitro* methods.

In vitro tools can be used to evaluate the molecule's thermal and chemical stability using various techniques. For example, the stability of the drug can be determined using size-exclusion chromatography (SEC) analysis after high-temperature treatment in low pH conditions. At present, these *in vitro* analytical tools are generally more accurate in predicting the molecule's stability and developability than *in silico* assessments.

Challenges in Formulation Development

During formulation development, feasibility studies can help select optimal candidates but there are still a number of challenges that can arise throughout the process. Expertise and experience are needed to identify these challenges early and to solve them with minimal disruption to the project.

- **Visible Particle Issues**
  One of the biggest challenges that formulation developers will encounter is the need to overcome visible particle issues. This includes formulations having visible particulate, sub-visible particulate, turbidity, and opalescence. These phenomena can occur with various root causes such as aggregation or precipitation. Having particulate matter in drug formulations is a significant problem, as these particles can lead to severe side effects including inflammation issues following injection.

Manufacturers must actively monitor the formula to prevent particle issues to reduce the risk to patients as well as ensure compliance with relevant pharmacopeia, which will often state that drug formulations should essentially be free of particulate and outline the acceptance criteria of sub-visible particles in terms of size.

In some instances when particle issues are detected during a screening step, there may be a need for the molecule to be re-engineered in the discovery stage. In most cases, however, particle issues in drug products can be prevented by identifying optimal conditions (such as pH, buffer composition, and excipient condition) via screening studies.

- **Missing Molecular Information**
  It is important to obtain as much information about the drug molecule as possible during a feasibility study, because understanding the molecular characteristics, such as the pI value, is critical in determining the optimal conditions such as pH or buffer constitutions for formulation.

Having the molecular characteristics readily accessible will prevent the need to conduct further screening activities and allow for more focus on finding the optimal solutions which will ultimately save time. It also means that developers are able to reduce the use of valuable drug substance material in these screening activities. If the information is available, communication between developers and those supporting

the formulation of the project will be essential.

- **Determining the Optimal Conditions**
  It is a common misconception made by many developers that conducting a wider array of various excipient, pH, and buffer type screening studies will help achieve better results in formulation development. In fact, as pH and buffer conditions are typically within a certain range for biopharmaceutical drug products, these discursive studies aren't always necessary. Studies that focus on narrowed-down, specific conditions are enough to find the optimal solutions.

Selection from a set of excipients, pH ranges, and buffers that are already widely used in similar biologic drug product manufacturing processes will often allow a company to find the optimal conditions and combinations more effectively. As the drug molecule's characteristics will heavily determine the optimal conditions, this approach will also rely on understanding these properties, such as their glycosylation and molecular structure.

- **The Need for In-process Controls**
  One of the most common missteps that can occur during the formulation development process is making an error when making reagent or buffer stocks. As the stocks will be used to make many all subsequent reagents or buffers at that step of the process, these errors can lead to a large amount of time being lost and work having to be repeated.

Human errors can be easily made when working with chemicals with very similar names, for example, switching the amount of sodium phosphate monobasic and phosphate dibasic when making a buffer stock. If such errors are made and undetected and go through the manufacturing process for drug substance and drug product, in a worst-case scenario, all formulation materials will become unusable.

To prevent this from happening, in-process controls (IPCs) must be conducted once the buffer or reagent is made. This could include measuring and recording the pH and conductivity of the stock upon completion to ensure it is within a set range. As errors are more likely to occur with under-trained employees, it is also important to rigorously train the employees to strictly adhere to all the necessary steps throughout the process.

Considerations When Scaling

With many challenges to overcome, it can be easy to forget to consider how scaling may impact the formulation processes, especially when moving from small scale to large scale. Mixing, filtration sizing, and compatibility in manufacturing scale-up processes are common stages in which issues can arise. For example, as the scale of the project increases, micro-filter size and pressure must be adjusted and optimised.

As a result, the conditions when scaling up should be considered from the start and throughout formulation development. It is therefore important to consider seeking support from manufacturers with experience and expertise working across a wide range of scales, that will be aware of these potential difficulties.

Achieving Faster Timelines

With an understanding of the challenges throughout formulation development and the methods that can be used to solve them, strategies can be designed aiming to achieve faster timelines to meet increasing demand.

One strategy that can be used to shorten the time taken for drug formulation is to unify processes from start to finish. This

will involve producing a standardised screening matrix and process for each type of molecule, including standardisation of the analytical tools used throughout screening steps.

Having a unified process can allow for more consistent formulation conditions to be determined and minimise risks from occurring when scaling up, as there will be confidence and experience with the standardised approach.

Ultimately, it is crucial to unify the process in a way that allows for tailoring to the molecule based on its characteristics. Utilising tools such as high throughput screening (HTS) systems that incorporate sample preparation and sample analysis to characterise the stability and activity of protein formulations will help to reduce timelines.

Adapting to New Drug Modalities

Advances and innovations in drug design and development have meant that formulation considerations must be made to a new wave of drug modalities, including Fc-fusion proteins, multi-specific antibodies, antibody-drug conjugates (ADCs), and gene therapy products such as mRNA vaccines. For example, formulation development for mRNA products must aim to ensure stability is maintained when in deep freezing conditions, requiring carefully selected "anti-freeze" excipients.

Similarly, ADC and recombinant proteins formulation will benefit from the production of appropriate formulation matrix sets with HTS systems to reduce the development timeline.

Moving into an era focusing on these previously unfamiliar drug modalities, it will become of increasing importance to be supported by those with formulation expertise and experience identifying formulation challenges.

A Look to the Future

In the future, it is likely that the high demand for speed in formulation development will continue. As improvements in formulation techniques advance, there will also be higher expectations of the final product.

Viscosity control throughout the process will make way for high concentration (>100 mg/mL) and ultra-high concentration (>200 mg/mL) formulation development. In protein formulations that are highly concentrated, viscosity increases due to enhanced interaction between the molecules. This increase in viscosity could result in injectability and product quality issues. Therefore, control of viscosity throughout formulation will become even more crucial.

In-depth studies on the delivery system will also become increasingly important with highly viscous drugs. Challenges surrounding the safety and convenience of the patient can arise, as injection of highly viscous drugs has been associated with cannulas being pushed out and syringes breaking if not designed carefully.

Key Lessons

Formulation development is associated with a wide array of challenges and hurdles that biologic drug developers must overcome to meet the demand for speed to market. Having a strong understanding of the characteristics and properties of the molecule is essential during formulation and will rely on strong communication with those manufacturing the product and carefully designed feasibility studies.

With new drug modalities on the horizon, support from dedicated contract development and manufacturing organisations (CDMOs) with extensive formulation experience will become increasingly important. With well-applied formulation strategies, these organisations can ease the process from start to finish, from small to large scale, while delivering speed to market without compromising quality.

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