

Achieving Faster Investigational New Drug Timelines with a Robust Cell Line Development Strategy

Technological advances in drug manufacturing equipment and process optimisation play a significant role in increasing speed to clinic of critical biologic drugs. Although implementing new technologies and strategies can shorten drug development and manufacturing timelines, there is still one area that is consistently time-consuming: cell line development. Even with well-established automated platforms, it typically takes three months to complete cell line development (CLD) while working towards an Investigative New Drug (IND) filing.

In this article, Youlim Kim, a Lead Scientist at Samsung Biologics, explores the challenges associated with CLD and offers an expert look into the tactics contract development and manufacturing organisations (CDMOs) can employ to shorten commercial timelines while preserving quality and yield.

The Growing CLD Market

Consistent growth in the antibody therapy market has been largely driven by the rising demand for monoclonal antibodies (mAbs), bispecific antibodies, recombinant proteins, and vaccines. However, development of these therapies targeting a vast array of therapeutic areas, including oncological, autoimmune, and infectious diseases can be complex and challenging, particularly CLD. Producing stable cell lines and avoiding inherent contamination risks in upstream and downstream development are common areas where difficulties can arise.

Subsequently, developers of antibody therapies looked to those with experience and expertise in offering CLD services for support. As a result, the market for CLD services has grown at a double-digit compound annual growth rate (CAGR) and is expected to reach \$1.7 billion by 2028.¹ Technological advancements in cell line engineering and screening techniques are also factors that are set to fuel this growth.

A Drive for Faster CLD

Despite the increasingly advancing capabilities

of biopharma's CDMO partners, CLD remains to be an area with both technical and operational challenges. Currently, best practices will often rely on processes that are manual, laborious, and time-consuming. One example of this is the use of selection markers for gene integration that require thousands of clones to be extensively screened.

For biopharma's CDMO partners, embracing technical innovation and achieving operational excellence will be the key to shortening the typical 3-month timeline taken to complete CLD when filing IND applications. By optimising protein expression platforms and developing cell lines that can accommodate an accelerated approach, patients will receive essential therapies faster.

A Robust CLD Program is Key to Acceleration

When striving to achieve faster CLD processes, it is important to develop a robust CLD program that aims to not only shorten timelines but to maintain yield, stability, and product quality. It must also ensure that regulatory compliance is upheld.

Identifying the fastest processes capable of achieving IND approval while providing high product quality requires an appreciation of the balance needed between speed and quality. The program should optimise CLD, increasing the specific productivities of often difficult-to-express proteins while improving titer, cell growth, and cell viability for commercialisation.

When building a CLD program, developers should consider introducing new screening technologies, optimising cell culture conditions, and developing new cell lines to maximise CLD output and achieve accelerated timelines.

Start by Choosing the Right Cell Line

Developing a robust CDL program relies on selection of the best expression host system for protein product expression. There are many different types of expression host system that can be used when developing and manufacturing biologics, including mammalian, bacterial, or fungal cells. However, mammalian cells provide unique characteristics to the molecule that

often cannot be achieved by lower-level organisms like bacteria and fungi:

- **Protein folding and assembly**

Folding and assembly of human proteins like mAbs into the right conformation is more likely to be achieved by mammalian cells, which will have cellular components and enzymes that more closely resemble the native host.²

- **Bond formation**

The disulfide bonds of antibodies must be formed in oxidizing conditions. In gram-negative bacterial expression systems like *Escherichia coli*, the reducing conditions of the cytoplasmic compartment will result in the formation of non-functional protein aggregates.²

- **Glycosylation**

As glycans attached to mAbs impact their pharmacokinetics, efficacy, and safety, correct glycosylation of the molecule is of utmost importance.² However, this post-translational modification (PTM) cannot be achieved by prokaryotic cells, including bacteria.

If the expression system chosen cannot properly fold and assemble the protein, form the bonds needed or conduct essential PTMs, there will be no viable product. Consequently, the potential for success in CLD and complex biologic production when using unicellular organisms is often not as high relative to mammalian cell line platforms. As a result, reliable mammalian cell lines, like Chinese Hamster Ovary (CHO) are often the ideal cell system to produce a variety of therapeutic proteins.

An Ideal Expression system: CHO Cell Lines

CHO cell lines are commonly used in the production of mAbs and bispecific antibodies, as they can not only express proteins with the correct quaternary structure but have many other advantages:

- **Relatively easy culturing**

As CHO cells can grow well as suspension cultures and have a high tolerance to a range of culture conditions, including pH,

pressure, and temperature. This allows improvement of safety and stability profiles as growth conditions can easily be adapted.

- **Ideal for scalable manufacturing**

The ability of CHO cells to grow as suspension cultures means that they are ideal for scalable manufacturing, avoiding the contamination risks and laborious manual processes that can be associated with adherent cell cultures.

- **High productivity**

By optimising and engineering CHO cell lines, developers and manufacturers can achieve a high yield of high-quality recombinant proteins.

- **Similar pharmaceutical activity and biocompatibility**

As CHO cell lines are capable of proper PTM, including glycosylation, that is similar to those in humans, they are able to produce biosimilar human products with biocompatibility and comparable pharmaceutical activity.

- **Widely available engineering tools**

The CHO cell line is well-characterised and has been widely understood for many years. As a result, there are many tools for CHO cell line engineering that are commercially available.

- **Well-recognised by the FDA**

As CHO cell lines have been used to produce around 50 biotherapeutics already approved in the U.S and EU, the FDA is very familiar with these expression systems.

Optimising CLD further with CHO

Building a CLD program around the use of an expression system like CHO will clearly provide many advantages. Optimising CLD further to produce a highly developed cell line is the key to forming a robust CLD program that balances high quality with accelerated speed. There are many different techniques that could be employed to shorten CLD timelines and improve efficiency:

- **Use proprietary CHO cell lines**

Many CDMOs have developed and engineered their own proprietary CHO cell lines to further optimise their CLD. With this approach, manufacturing-ready cell lines offering high growth rate, yield, and productivity can be generated.

- **Optimise upstream processes**

By optimising upstream processes, including cell culture processes for large-scale production, developers and manufacturers of antibody therapeutics can start CLD and production from a position of strength. Optimisation should be carried out with the aim of achieving high specific production rate for qualified protein expression and secretion. Using customised cell culture media and preparation of the molecule and formulation for commercial manufacturing can further strengthen this starting position.

- **Consider improving facilities, capacity, and technologies**

Implementing advanced analytical technologies and high-throughput tools can also help to shorten CLD timelines. For example, high-throughput affinity capture technologies can accelerate cell isolation, screening, and selection with automation. Using single-cell printing techniques for cell sorting, or advanced artificial and machine learning can also be used to increase production speed.

Outsourcing to Further Strengthen Development Programs

Increasingly, the best-performing development programs are those that outsource CLD to strong partners with experience and expertise with similar molecules. This is because working with a single, end-to-end CDMO partner can alleviate or eliminate the disconnect between different stages of CLD. Partnering with specialists can improve CLD programs by:

- Providing access to innovative and efficient CLD platforms to maximise process and quality outcomes
- Bringing cost efficiencies with new ways to manage and curtail costs that do not compromise product quality or patient safety
- Alleviating internal resources and allowing developers to focus on core competencies

Always Keep IND Goals in mind

As each phase of CLD will have differing and sometimes competing priorities, it is important to always come back to the larger IND and BLA development goals throughout optimisation. From the onset of CLD program development, all aspects of the product lifecycle must be considered to identify areas for optimisation early

and determine areas where time could be saved.

Building a robust CLD program with IND and BLA goals in mind can offer developers key elements that will allow them to start future programs more effectively, regardless of strategy or partner. The collaboration of key project stakeholders involved in development of the program will help to build a thorough understanding of the characteristics of the model as well as the program needs.

The development of well-defined communication and issue-resolving protocols can also be achieved more easily with a robust CLD program in place, allowing for real-time project transparency. Drug programs are also more likely to meet challenging end goals and criteria with a program emphasizing transparency and enabling critical data to be accessible and sharable.

Key lessons

Balancing high quality and accelerated timelines in CLD is the key to achieving faster IND and relies on the careful optimisation of all areas in the process. It is important to not focus too heavily on one aspect or analytical area when building a robust CLD program. With expertise across all fields, leading CLD service providers are well-placed to optimise processes holistically and pave a faster and more efficient path to IND filing.

REFERENCES

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