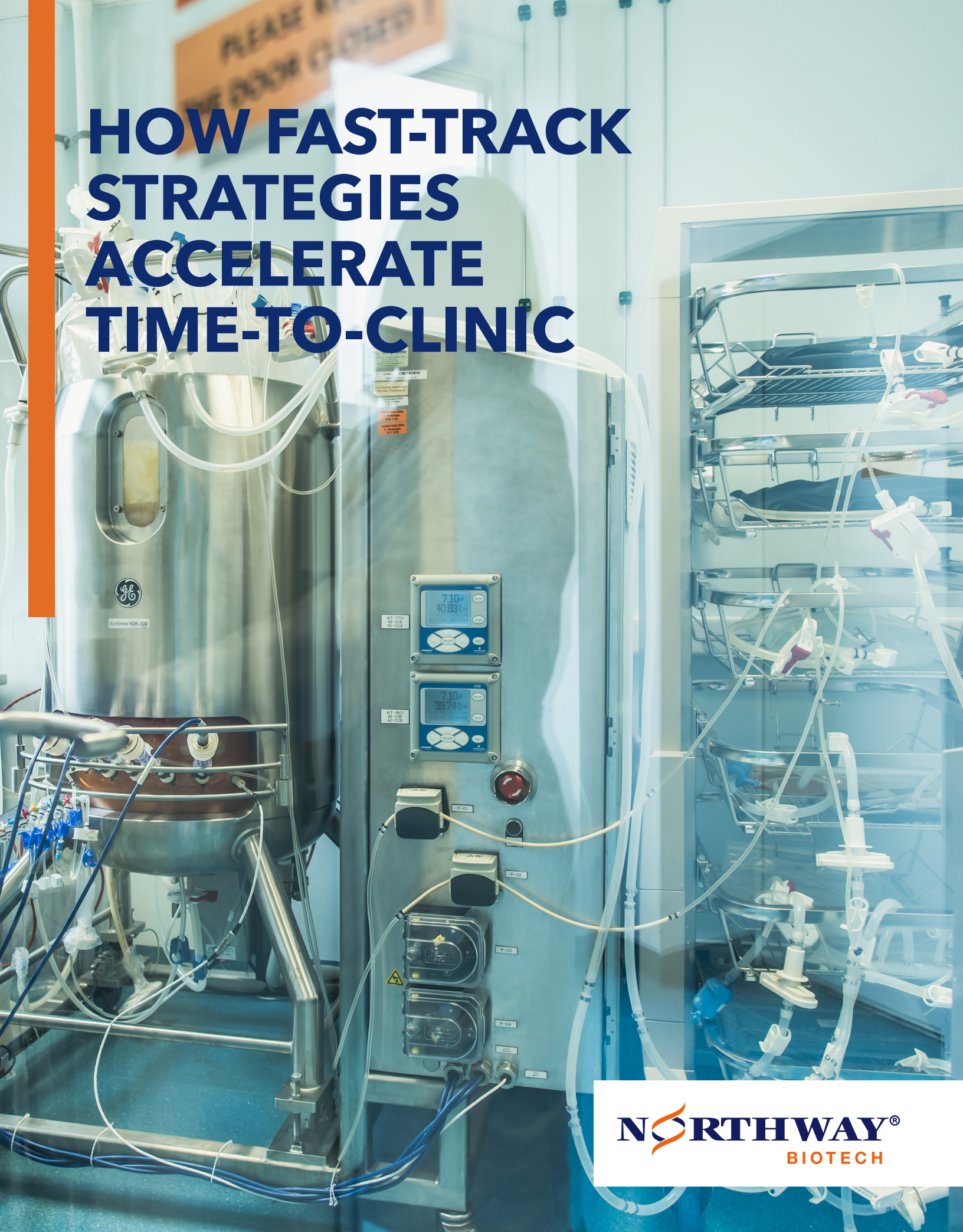
HOW FAST-TRACK STRATEGIES ACCELERATE TIME-TO-CLINIC



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HOW FAST-TRACK STRATEGIES ACCELERATE TIME-TO-CLINIC

Biopharmaceutical sponsors can minimize to-clinic timelines by using innovative development strategies that trade potentially increased risk for time savings.

Pharmaceutical sponsors' ambitious development timelines rarely align with the normal duration for biologics cell line, upstream process (USP), downstream process (DSP), and analytical methods development and scale-up. Typically, the timeline duration is based on providing material to support an investigational new drug (IND) filing with the FDA or its EU equivalent, a clinical trial application (CTA).

Sponsor timelines may reflect an attempt to beat competitors to first-in-clinic or a need for clinical data to drive additional funding. Whatever the reason, the application of various fast-track approaches can shave weeks or months off development timelines, trading increased risk for potentially extraordinary rewards. Fast-tracking pushes development teams forward with less data than would be available following a traditional timeline and is driven by two key strategies: decoupling activities and following a critical path.

Decoupling requires examining every development activity and determining what can be conducted in parallel, versus sequentially. Through this exercise, a critical path emerges that provides a logical baseline for decision-making (i.e., does this approach make sense for us in the context of our established critical path?).

WHICH MOLECULES AND PROCESS STEPS CAN BE FAST-TRACKED?

In principle, fast-tracking is straightforward, but its execution requires decision-making under pressure (based on limited information), supported by agile communication and coordination between a sponsor and its CDMO partner. Fast-tracking strategies often are guided by the partners' combined development experience with similar molecules. However, risk varies based on individual molecule characteristics, which can ultimately impact expected timelines. For example, standard monoclonal antibodies (MAbs) can be inserted into a platform process, but some molecules require development and/or optimization to meet the sponsor's desired productivity and product quality attributes.

A platform MAb process could attempt to produce different MAb proteins with minimal parameter changes and still achieve acceptable results in terms of both productivity and purification to meet clinical trial requirements. More complex molecules require additional development effort, more experiments, and potentially extra unit operations (i.e., major steps in the production or purification process). Such molecules are more difficult to accelerate versus a standard MAb, and are subject to different levels of fast-tracking.

Still, no molecule's behavior is 100 percent predictable. But, sponsors know early in the process – generally via the purification step known as affinity chromatography – whether a fast-tracking approach is going to work as expected for the initial capture step.

In general, USP activities take longer due to the required culture time. However, they can be more conducive to fast-tracking than DSP activities, since the latter contain more unit operations and the starting material can significantly impact the unit operation outcome.

Considering cell line development, does the sponsor want to move forward with a single clone or several clones? Growing numerous clones simultaneously allows developers to make a comparative choice based on titer expression or another attribute. Whatever the choice in clone selection, developers can further compress the timeline by deciding the extent of, or complete absence of, media screening and optimization of feeds. If abbreviated media and feed screening are selected, or bypassed completely, the sponsor must be willing to accept the resulting titer levels.

Downstream opportunities for fast-tracking generally are limited by quality attributes with which a molecule must comply (e.g., for an injectable: residual host cell DNA, residual host cell protein, bioburden, endotoxin). These qualities typically are not negotiable with regulatory agencies. However, previous experience with molecules of similar characteristics (such as the protein's isoelectric point – the pH at which the molecule has a net-zero electrical charge) may allow for predictive behavior during chromatographic separations. This, once again, allows the sponsor and CDMO to choose between fast-tracking or a more typical and thorough purification development plan.

Ultimately, fast-tracking options selected can affect the sponsor/vendor contract. Say the partners agree to execute a platform approach, making assumptions about titers. They discover they can achieve 1 g/L. Given the cost of cGMP runs, does it make sense to forge ahead or go back to the drawing board? Increasing the batch size or conducting multiple runs are more viable options than restarting developing or picking a different clone. Depending on the CDMO partner, other monetary commitments (e.g., cancellation fees) may require consideration should a sponsor abandon the higher risk of fast-tracking and pursue additional development work to achieve a more robust production and purification process.

FAST-TRACKING IN PRACTICE

Fast-tracking can begin with selecting the clone for cell line development. Advanced equipment (e.g., Verified In-Situ Plate Seeding, or VIPS™) can be used to more quickly arrive at the desired research cell bank or master cell bank for implementation into the platform. While some CDMOs have invested in this more state-of-the-art equipment, whose principal value is timeline reduction, many CDMOs still use the more antiquated technique of limited dilution cloning.

For example, with limited dilution, it is necessary to perform two rounds of seeding across a minimum of 10 plates/round to ensure the cells picked from these colonies (for further downstream processing) have derived, statistically, from a single clone. In contrast, through real-time z-stack image-based clonal detection, VIPS reduces the number of plates necessary to achieve a higher efficiency in assurance of single cell clonal derivation (versus limiting dilution) and reduces the overall workflow process. Workflow efficiency is improved by reducing the number of plates to observe/track/manage and the number of rounds of seeding (down to a single round) to achieve high confidence in clonal derivation. Since two rounds of seeding take about three weeks (versus one round of seeding, which takes about one week), up to two weeks are saved through this process alone.

Next, initial purification takes place, typically involving some form of chromatography, either binding the product or binding impurities. Many CDMOs have a library of other MAb projects that can be referenced to inform and pursue a fast-tracking effort.

For example, a sponsor project's early clone work can be compared to other molecule development data previously executed, provided confidentiality is maintained, enabling the sponsor to make more educated decisions with limited data sets. Using a platform approach, developers may be able to predict that a clone titer of 0.4 g/L in early shake flask studies correlates with 1 g/L or more in a fed-batch bioreactor, based on previous experience with molecules of similar characteristics and the cell line selected. By comparing the molecule against a library of previously generated data, recommended parameters for cell growth and protein expression can be suggested, thus reducing the timeline.

For MAbs, the first and most impactful purification step typically involves chromatographic separation utilizing resin containing an immobilized Protein A ligand, which binds the constant region of the MAb while other proteins flow through the resin to waste; this is an example of affinity chromatography. Positive results generally indicate the platform will be successful for a fast-track approach. If binding does not occur, it is an early indication that a more rigorous development approach will be necessary, likely abandoning the fast-track timeline in favor of reducing risk and achieving necessary purification goals.

Subsequent chromatography steps are generally referred to as "polishing" and are aimed at removing any remaining host cell protein (HCP), residual host cell DNA (rDNA), or product variants and aggregates. Again, leveraging past experience can equate to running only a few experiments to show the unit operation is effective.

From there, a CDMO can employ a number of additional fast-tracking strategies. Skipping the engineering run – the first time a run is conducted at production scale but with less stringent execution requirements – or conducting that run at an intermediate scale is common. More innovative approaches focus on USP and DSP activities than can be completed in parallel to consolidate the timelines.

For example, the process requires material to verify the platform works. Cells need time to grow – a mammalian upstream cell culture run typically takes 25 to 35 days – so normal timelines initiate DSP after USP because material is needed from USP to execute DSP. However, theoretically, the two can be run in parallel if material is available sooner; process development does not need to occur one function at a time. One option to consider is rapid transfection and growth of a modified CHO cell line (in less than two weeks) to generate material for DSP testing and analytical method verification while the production clone is being built.

Analytical methods (e.g., qualification and verification) represent another significant gating factor. A CDMO must astutely manage how much material is needed and who needs it as well as how different departments' use of material will be coordinated. How effectively the CDMO manages various parameters – including the time it takes to physically grow cells, its management of the different teams utilizing those cells, and its oversight of other internal activities supporting these processes – is vital to fast-tracking execution.

It also warrants mention that COVID stands as its own entity in the context of fast-tracking. In general, vaccine programs have been expedited and developers have been willing to accept more risks than they normally would. Even regulators have looked at ways to accelerate timelines. For example, demonstration of monoclonality normally is a vital criterion, but U.S. and EU regulators have explored parameters that might be changed to promote faster-to-market solutions that address the pandemic without introducing excessive risk to the patient population. Essentially, the regulatory bodies have looked at every aspect of the approval process and created waivers that normally are not considered.

FINAL THOUGHTS

Fast-tracking time-to-clinic is, at its heart, a risk-versus-reward proposition. However, sponsors can take steps to minimize risk while markedly improving their chances of success. This starts with selecting a CDMO partner that prioritizes your proposal, adopting a fast-tracking mindset from the start.

Specifically, the initial proposal should be comprehensive and revisions should be turned around quickly. The CDMO must be able to satisfy the sponsor's executive team in terms of timeline, and its QA team in terms of the standard operating procedures (SOPs) guiding fast-tracking (i.e., how is this timeline possible from a technical and safety standpoint?).

Further, the CDMO must get to work quickly. This can be facilitated by creatively structuring the contract (e.g., a hybrid approach that works off terms & conditions initially, allowing process development and verification to occur in parallel while the MSA is being negotiated – as long as it is in place by the start of cGMP activity). This capability alone can save weeks to months.

Being fast out of the gate also requires a CDMO with reliably accessible key raw materials. Ideally, development allows for the screening of a variety of medias, but in a COVID-altered world, those materials must be in stock already or easily orderable/attainable. In that same vein, the CDMO's technical team must be quickly available (e.g., able to be assembled and on a call in 24 hours to facilitate fast-track decision-making).

Next, the sponsor and its CDMO partner must exhibit a clear understanding of the process flow diagrams for both the USP and DSP in a variety of fast-track scenarios (Figs.1-3). Product release depends heavily on this agreement regarding what can and cannot be fast-tracked.

For example, two weeks of sterility testing must take place after the drug product is generated. That two-week period is unwavering on the Gantt chart, but how fast can the team write reports once they secure the data? Fast-tracking can complete the task in a week or two, while a traditional timeline may span more than four weeks (pushing back release by three to six weeks).

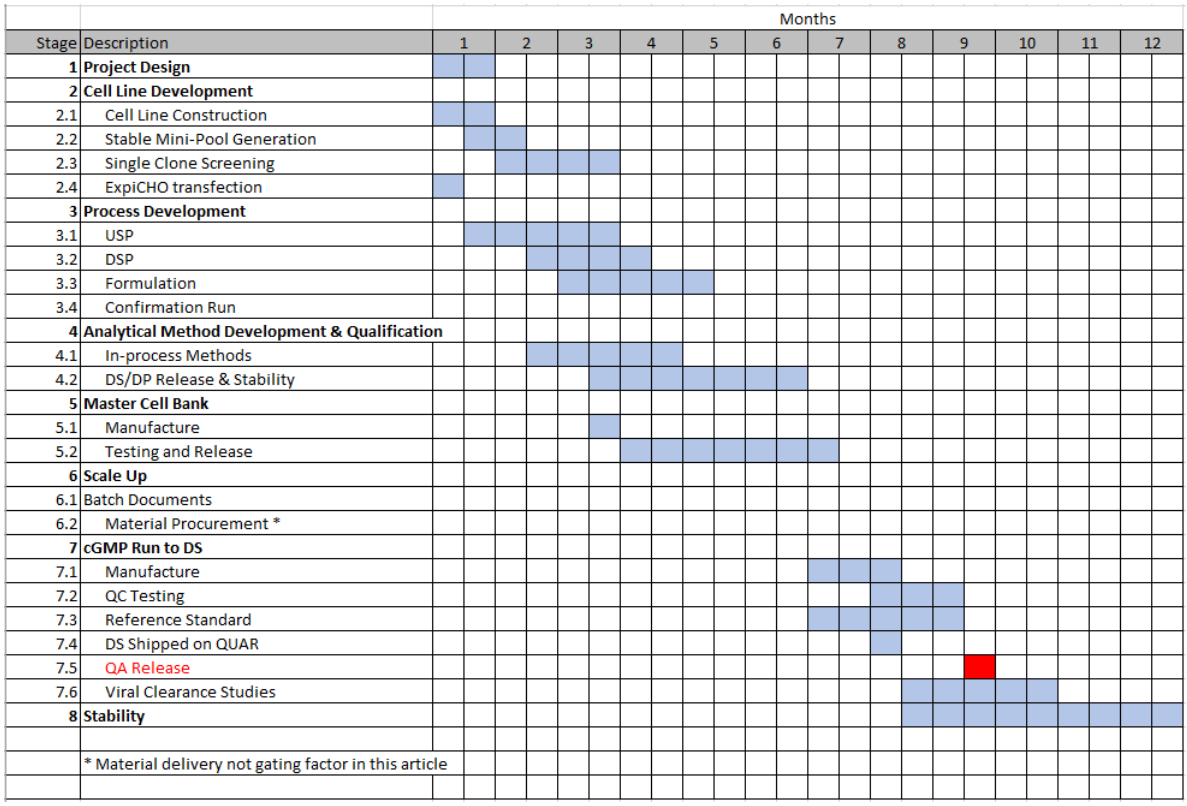

Figure 1 - Normal MAb Development Timeline

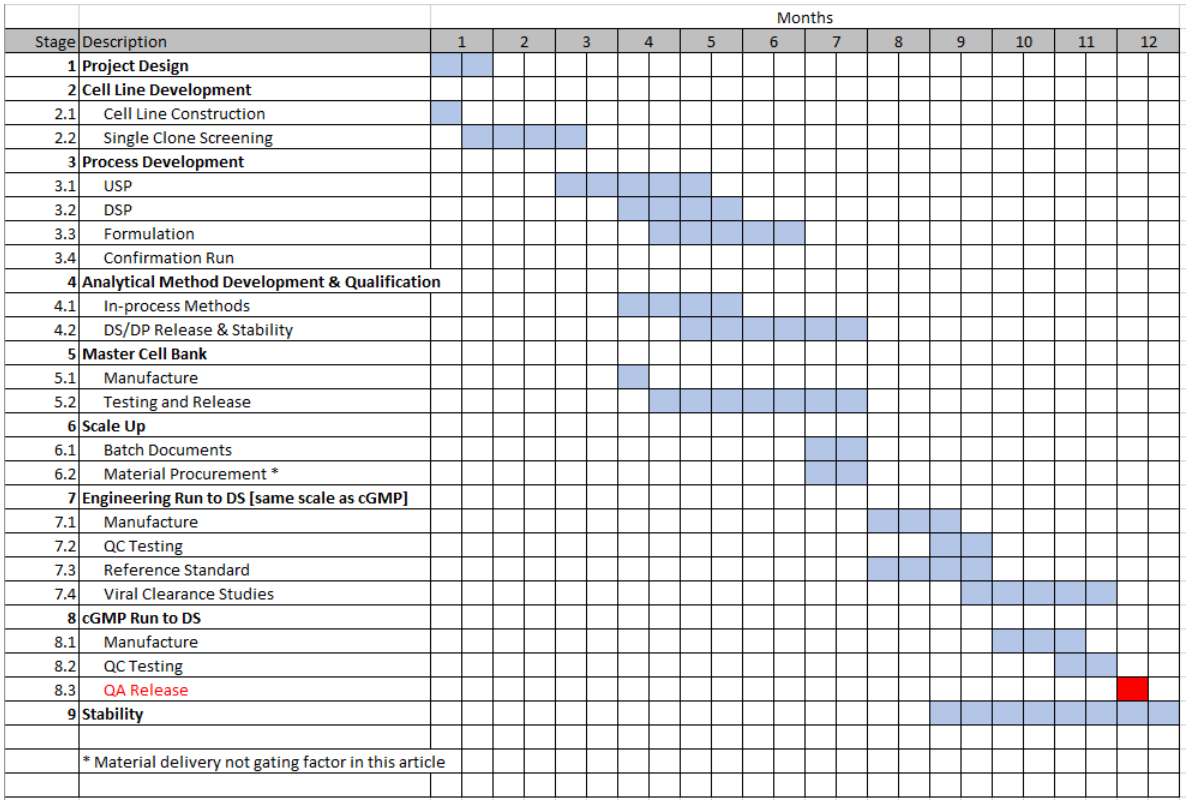

Figure 2 - Accelerated MAb Development Timeline

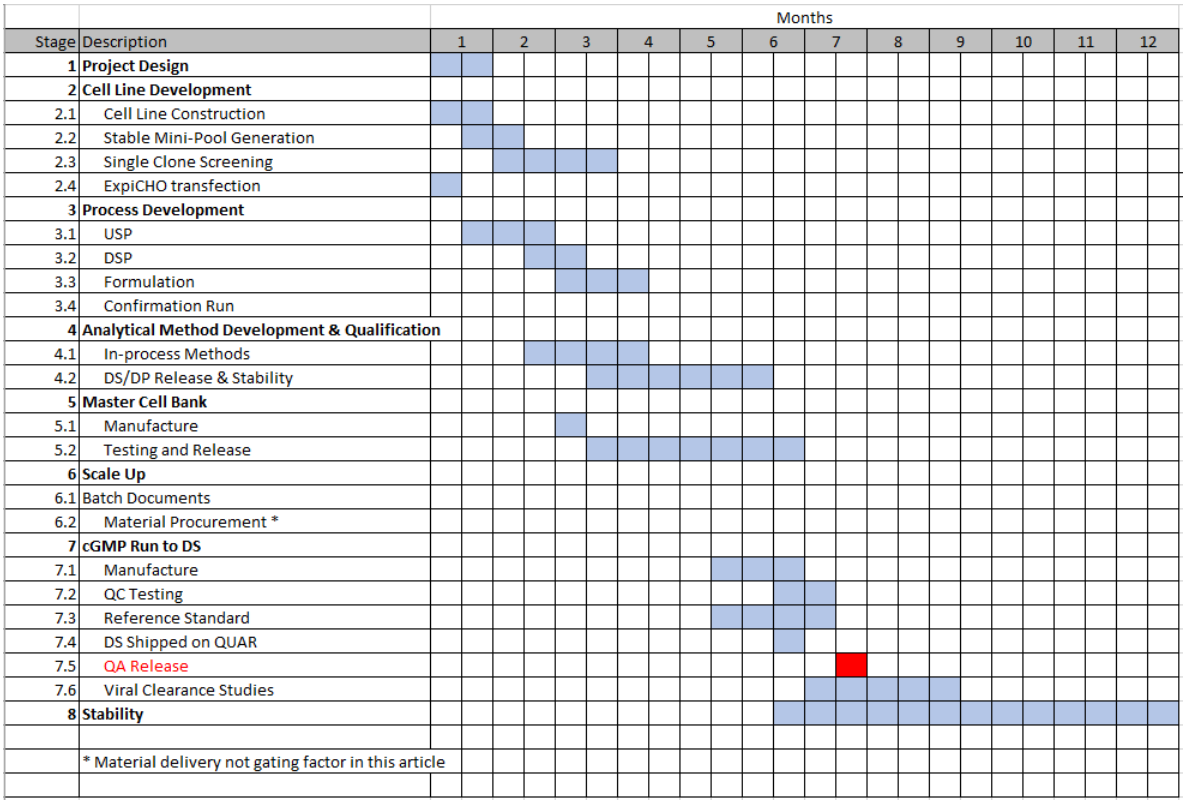

Figure 3 - Super-Fast MAb Development Timeline

Outsourced activities – key for aspects like virus clearance studies (VCS) and master cell bank (MCB) characterization – also should be considered early. VCS vendors also are likely to be working within compressed timelines, and regular contact helps ensure you do not accelerate your timeline only to find they have no slot available for your project. This communication and planning is facilitated by agile business development and project management personnel, as well as a deft technical team able to maintain those relationships and initiate those conversations.

Finally, sponsors must understand and embrace that fast-tracking requires steadfast commitment and "it is what it is" – you're not going to get an optimized amount of material, but you can get enough to supply Phase 1 needs. Process optimization can follow once that initial goal is reached. And, increased time savings usually equate to increased risk.

Regarding sponsor and CDMO commitment – as well as dedication to collaboration – consider that a multitude of documents will need to be reviewed by various parties, all with very strict timelines for turnaround of revisions. There is minimal time for back-and-forth. A strict adherence is necessary, not just to the lab work, but to the review of documentation and, ultimately, agreeing on the final protocol/SOPs. Thus, while the CDMO is tasked with much of the boots-on-the-ground work, the sponsor is equally responsible for maintaining that fast-track timeline, particularly in terms of timely delivery of information.

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