The current economic crisis, increasing competition, and the need to make healthcare more affordable combine to present formidable challenges to today's biopharmaceutical industry. By 2015, spending on prescription medicines in the U.S. alone is forecast to be approximately $450 billion, representing more than 10% of total U.S. healthcare expenditures. Therapeutic monoclonal antibodies have now become the dominant component of the biopharmaceutical market with combined 2008 revenues estimated to be nearly $30 billion. Continued development of this exciting class of products is expected to continue to drive the overall sales of biopharmaceutical products in the future.

BioProcess Technology Consultants recently published The Development of Therapeutic Monoclonal Antibody Products, a comprehensive report outlining the complex technical, regulatory, and strategic Chemistry, Manufacturing, and Control (CMC) activities necessary to successfully advance new monoclonal antibody products from discovery to First-in-Human clinical trials and the market as quickly and economically as possible. This article, based in part on the report, will summarize the overall costs and timing for development of a new monoclonal antibody product and outline the critical development, manufacturing, quality, and regulatory activities required to support the successful filing of an Investigational New Drug (IND) application to initiate human clinical trials.

CMC development is one of the most critical and time-consuming tasks required to enable human clinical testing of a new monoclonal antibody candidate. This task includes the construction and testing of a production cell line and manufacturing process for production of the product as well as development of suitable analytical methods to characterize the antibody and ensure that it is safe and has the desired functional properties. The numerous, interdependent CMC activities required to advance a monoclonal antibody candidate from discovery to clinical trials and the estimated overall costs of these activities are outlined in Table 1. Many of the activities included in Table 1 must be substantially completed before animal toxicology studies can be performed, since these studies must use product that is produced using essentially the same process that will be used to make material for the human clinical trials. Detailed project planning and management is essential to coordinate these multiple activities and ensure technical and regulatory success.

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Table 1: Estimated cost of IND-enabling CMC activities

<table>
<thead>
<tr>
<th>Activity</th>
<th>Estimated Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Analytical development and qualification</td>
<td>$1,050,000</td>
</tr>
<tr>
<td>Cell line and upstream process development</td>
<td>$600,000</td>
</tr>
<tr>
<td>Downstream process development and viral clearance validation</td>
<td>$900,000</td>
</tr>
<tr>
<td>Formulation development</td>
<td>$300,000</td>
</tr>
<tr>
<td>Bulk drug substance manufacturing, including stability studies</td>
<td>$3,300,000</td>
</tr>
<tr>
<td>Final drug product manufacturing, including stability studies</td>
<td>$550,000</td>
</tr>
<tr>
<td>IND Preparation (CMC Section)</td>
<td>$100,000</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>$6,800,000</strong></td>
</tr>
</tbody>
</table>

Since the CMC activities described here are on the critical path to a successful IND filing, it is essential that they be completed as quickly as possible to facilitate the initiation of human clinical trials. A typical timeline for CMC development activities required prior to filing an IND is shown in Figure 1. Unlike other therapeutic recombinant proteins, the commonality in molecular structure of monoclonal antibody products enables the use of common platform technologies or processes for both upstream and downstream processing. Therefore, the timeline shown in Figure 1 is based on the assumption that development is carried out in the context of a reasonably well-established set of analytical methods for product characterization and QC testing and release and the use of platform processes for upstream and downstream processing, with full process optimization and validation being performed later in development. The use of platform processes allows the rapid production of monoclonal antibody products for human clinical evaluation.

Figure 1 provides a useful framework for understanding the interdependencies of the various tasks that must be completed prior to filing an IND and initiating human clinical trials for a monoclonal antibody product. Each of the major groups of tasks listed in Figure 1 is generally performed by distinct resources either within a product development company or by a contract service provider. The technical and business details of any given monoclonal antibody product development program may result in some variance from this typical timeline. Some companies have reported CMC development timelines as short as 10 – 13 months, but it is more typical for these CMC development activities to take at least 18 months to complete at a cost of approximately $7 million.

**Process Development Activities**
The first CMC activities that are required for monoclonal antibody development are the development of suitable analytical methods and the generation of a production cell line for the
Development of a suitable genetically-modified, engineered cell line capable of producing a monoclonal antibody with sufficiently high productivity is one of the most time-consuming CMC development activities. Using traditional selection methods, cell line development can take as long as nine months to complete. However, many technologies are currently available that improve the speed of cell line development, producing cell lines with sufficient specific productivity for manufacturing in as little as three to six months. At least some analytical methods must be in place prior to initiation of cell line development to insure that the right product is produced by the candidate cell lines and the final selected cell line. As the development program progresses, additional analytical methods are normally developed to support cell culture and purification development, quality control testing, and characterization of the bulk drug substance and final drug product.

Meeting the necessary purity levels is an absolute regulatory requirement, while product yield is primarily an economic concern for the company developing the product.

The downstream process consists of a series of recovery and purification steps to enable the antibody to be purified to homogeneity. The antibody produced in the upstream process is separated from impurities (substances related to the desired monoclonal antibody product or process that are undesirable in the final product) and potential contaminants (substances that are not intended to be in the process, product, or intermediates but which may be present and require removal) to levels sufficient for delivery to a patient. The development of a suitable recovery and purification process for a monoclonal antibody focuses on two main technical aspects — the effectiveness of the removal of impurities and contaminants (i.e. the product purity) and the yield of the product (the percent of the active antibody product present in the bioreactor batch that is recovered in the final bulk drug substance). All processes involve tradeoffs between yield and purity, so the major overall goal of downstream process development is to insure that the purity is sufficient for the monoclonal antibody product to be safe for its intended use, while simultaneously maximizing yield. Meeting the necessary purity levels is an absolute regulatory requirement, while product yield is primarily an economic concern for the company developing the product. The purified monoclonal antibody solution resulting from the recovery and purification process is referred to as the bulk drug substance.

Other CMC development activities that are essential to enable a successful IND filing include formulation development and stability testing. The antibody must be formulated to ensure that the proper dose of active antibody reaches the proper site of action in the body upon administration to the patient and that the drug product is stable during storage. Formulation development should be initiated as soon as product is available, even product from process development activities which may not be fully representative of the final process.
To select an optimized formulation, the monoclonal antibody product is prepared in a number of different formulations and subjected to accelerated storage conditions. Analytical methods that are stability-indicating are used to determine which formulations are best for maintaining antibody structure and function. Data supporting the structural and functional stability of an antibody must be generated prior to an IND filing, and the stability program must continue for as long as a specific lot of antibody product is used in the clinic.

Scale-up and Manufacturing For First-in-Human Clinical Trials

After process development is completed, the upstream and downstream process for production of a monoclonal antibody product must be scaled-up to the intended manufacturing scale for production of early-stage clinical trial material. Scale-up is required in order to produce sufficient amounts of material for clinical and other needs. For the production process, scale-up involves careful engineering and testing to ensure that the process performs as expected and the product is not adversely affected. Some scale-up activities can be performed in the development laboratories but to reach the final production scale, one or more engineering or demonstration batches are often produced at the intended manufacturing scale. These non-GMP batches are often produced in the GMP production suite and material from these studies is often used for preclinical GLP animal studies in support of an IND application and to produce a reference standard. The production of an engineering batch (or batches) enables final process optimization and resolution of any scale-up or production issues prior to the first batch produced under cGMP.

Following production of the bulk drug substance for clinical use, the antibody must be filled into vials or syringes to generate the final drug product for shipment to the clinic. The manufacture of a monoclonal antibody drug product involves three critical processes — formulation, sterilization, and aseptic filling of the product — shown schematically in Figure 2. In the first step, excipients such as buffering agents, stabilizers, or cryoprotectants are added to the bulk drug substance solution to ensure the stability of the product in the final container and the protein concentration is adjusted to the desired level for storage and administration. The formulated bulk drug substance is sterilized by filtration to remove all bioburden from the solution and produce a sterile product for parenteral administration. This sterile bulk drug substance is normally aseptically filled into pre-sterilized vials or syringes, although other containers, such as IV bags, are occasionally used.

The first commercial therapeutic monoclonal antibody product was approved in 1986 and more than 20 antibody products have been approved since then. Since monoclonal antibodies are such a dominant element in today's biopharmaceutical market, significant effort has gone into developing more efficient technologies and tools to enable higher titers, better yields in downstream processing, and more cost effective manufacturing processes that will impact the cost of goods of commercial products. Some of these technologies have already been implemented in existing commercial antibody manufacturing processes whereas other cutting-edge novel technologies are still finding their way into development programs.

The regulatory environment for biopharmaceuticals is constantly evolving. For example, as recently as 10 years ago most cell culture was performed in the presence of serum. Today there are advanced media formulations that enable initial cell transfection, cloning, selection, and culture in the bioreactor in the absence of any serum, and removal of serum from processes is now expected by the regulatory agencies. The requirements for purity and for viral clearance validation have also become more stringent in the past decade. These regulatory changes impact the cost and time needed to develop manufacturing processes for new monoclonal antibody products.

The critical CMC development activities for new monoclonal antibody products consist of a series of well defined steps which, when carefully managed and followed, enable companies to advance new monoclonal antibody product candidates into human clinical trials with a high probability of success. These activities normally require approximately 18 months to complete although advances in all aspects of process development may lead to some reductions in this timeline in the upcoming years.

References


