New Challenges for Biopharmaceutical Process Development

By John Curling

The U.S. Food and Drug Administration (FDA), through the Center for Biologics Evaluation and Research (CBER)/Center for Drug Evaluation and Research (CDER), has long identified that the development of biopharmaceutical products is becoming increasingly challenging, and is inefficient and costly. The agency has also commented that superior product-development sciences are needed to address the challenges — a statement that will affect vendors, biological product developers and manufacturers alike.

Critical Path

In essence, the March 2004 FDA document *Innovation/Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products* [1] presents to industry the seemingly impossible challenge of developing better (higher quality or safer) products faster at a lower cost. At the same time, the path and procedures from IND to marketing approval need significant modernization, within and between the regulatory agencies. Agencies need to embrace the many new and emerging analytical technologies that allow for a risk-based approach to product development, characterization, comparability and approval.

Over the last 25 years, advances in recombinant DNA and hybridoma technologies have led to the development of many modern biotechnology medicines. During this time, regulatory authorities, to assure quality and safety, and the industry, to protect intellectual property and market share, have held “the process defines the product.” Indeed, until the advent and commercial production of monoclonal antibodies, practically all processes were unique to the products for which they were designed. These processes, when compared to the pharmaceutical industry as a whole, are for small-volume products manufactured using multiple separation steps to achieve final purity, as well as impurity profile consistency. It is only with the expansion of the monoclonal antibody markets to high-dosage and high-patient-number indications, such as rheumatoid arthritis, that the industry has been forced to really scrutinize, with an economic eye, every aspect of development and manufacturing. The biopharmaceutical manufacturers are thus facing the challenges of migration to a “more-for-less” environment — maintaining quality and safety but reducing costs.

The agency “post-approval lot release” practice for biological products is being superseded by a more pragmatic approach as the well-characterized and “know thy product — know thy process” paradigms take effect. However, excruciatingly long clinical trials, final review and marketing approval still last up to three years. Manufacturers are therefore caught in the squeeze of an 80-per-cent failure rate before filing for an IND and entry into Phase I clinicals, and an 80-per-cent success rate after the initiation of clinical trials. At what point, then, is the manufacturer willing to commit to a manufacturing investment knowing that the early stages only see a one-in-five success rate?

Biogen Idec Inc. (Cambridge, MA) tackles the dilemma in a two-cycle approach. Up to IND filing, it is a race to get to the clinic with a reasonably defined product but with a process that is not yet economic. With a decision to go for clinical development, an entirely new phase is entered. Process and product development will then target a well-characterized product and an economic, strong and reproducible process, as well as the large-scale applicability of the process. Relatively new to the biopharmaceutical industry is the challenge of fitting the product and process to existing facilities, unit operation installations and schedules within the supply chain.

The two phases in the product development cycle can be illustrated by comparing the affinity chromatography step for initial capture in the production of Amediplase (Menarini Group, Florence, Italy), a tissue plasminogen-urokinase fusion protein. The standard affinity ligand used for the discovery process is compared to the specifically designed, synthetic ligand in the proposed production process. This latter mimetic ligand and adsorbent was developed by ProMetic BioSciences Inc. (Montreal, QC) at its Cambridge, U.K. R&D site using advanced computational and combinatorial chemistry (BioDrugs. 2002;16(5):378-9).

Process Analytical Technology

Two tools are being used to speed the process of technology transfer into manufacturing: PAT (Process Analytical Technology) and the development of platform technologies. The well-established quality axiom that “quality cannot be tested into products but should be built-in or should be by design” is now being applied with PAT as the operative mechanism of assuring quality, reducing failures and mitigating deviation during manufacturing.

Genentech Inc. (South San Francisco, CA) believes that PAT will help in achieving a common goal for regulatory agencies and industry through improved process knowledge. Similarly, Amgen Inc. (Thousand Oaks, CA) promotes the understanding of processes, stating that it is inversely proportional to risk. Additionally, thorough cognizance of the manufacturing process and the development path that led to it allows for flexible management of change. The ubiquitous use of on-line monitoring of processes in the biopharmaceutical industry forms the foundation for development of corrective measures in manufacturing, and the adaptation of at-line and off-line analytical procedures to PAT. Together with trend analysis and other computational methods, PAT is expected to contribute to process understanding and reduce risk associated with the impact of seemingly small process changes, such as the change of a vendor for a process ingredient.

Platform Technologies

Platform technologies are manufacturing operations that should be applicable to more than one biopharmaceutical, with the desired effect of eliminating process re-invention for each new product and reducing manufacturing investments. Concomitantly, the corporation will develop core technology programs off the process-development path. New technologies — which by definition need to provide cost savings, faster production, safer products and other benefits within the supply chain — can be introduced systematically. Monoclonal antibody manufacturing is the lead example of platform development with more or less standard unit operation sequences being used in downstream purification: feed stock clarification, antibody capture, polishing to remove host cell

proteins and residual DNA, and finally, formulation of the bulk active product prior to fill and finish operations.

Risk Management

After two years of work by multidisciplinary working groups, *Pharmaceutical cGMPs for the 21st Century – A Risk-Based Approach* [2] was issued by the FDA in September 2004 in its final form. The FDA's "guiding principles" will be risk-based orientation, integrated quality systems, international co-operation, strong public health protection and science-based policies and standards. These admirable principles, however, have to be translated into the "nitty-gritty" of product and process development. The FDA notes that implementation will require "a highly educated and well-trained and integrated team of individuals throughout the FDA . . . "

Indeed, the same will be required of an industry that is characterized by exceptionally high educational and professional standards. Universities and higher educational institutes throughout the world will be challenged to provide the industry with the appropriate academic, yet industry-oriented skill sets that will drive biopharmaceutical development in the future. There is a never-ending need for pure scientific discovery and development, but an onus and continuing challenge to the practitioners of biotechnology to cross the academic–industry boundaries.

Although a risk-based approach, or risk management, is identified as a key attribute of the FDA, risk management and focus on critical quality issues and their relevance to product safety and efficacy will pervade the entire industry over the coming years. Changes, particularly manufacturing process changes, have always been seen as risks, leaving the proven for the possibly unknown. The combination of platform technology development and implementation of comparability protocol supported by PAT should facilitate change for the better, as well as the introduction of the new technologies.

Product Development Sciences

Upstream and downstream process development would not be possible without the significant resources spent by vendor companies, academic departments and institutes that provide the fundamentals for applied research. The superior product development sciences will be a result of meeting challenges to continue to increase expression levels in mammalian cell culture systems and the development of more specific and scaleable purification technologies, almost certainly based on chromatography. Also, protein engineering, to provide biopharmaceutical product attributes, such as extended half-life or improved targeting, are likely to play a significant part in new product development.

Such challenges can only be met if the development of exceptionally fast and specific analytical techniques keeps pace with separation process development. The information generated by parallel, high-throughput techniques and PAT will need continued investment in nanotechnologies and rapid, sophisticated data handling, reduction, analysis and presentation.

More For Less

The Tufts Center for the Study of Drug Development (Boston, MA) reports that drug-development costs in the pharmaceutical and biopharmaceutical industries combined are approaching $ 1 billion US ($802 million US in Y2000 dollars). The FDA cites the Bain drug economics model — produced by Bain & Co. Inc. (Boston, MA) — from 2003, showing a cost increase of 55 per cent for the years 2000-2002 compared to the period 1995-2000. The bulk of this increase lies in the Phase II and Phase III stages and marketing approval parts of the product-development cycle. Although this may only marginally affect biological process development, all of the technologies mentioned here should lead to risk minimization and possible savings in clinical trials.

The regulatory pathway is undergoing major change as the efforts of the ICH (International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use) to globally harmonize product development, regulatory submission and quality take effect. Harmonization within the European Union shows major benefits can be achieved. Cost savings for agencies, as well as sponsors are an expected outcome.

With high costs, particularly in North America, generic or follow-on biologicals present a significant opportunity as well as a challenge globally. The World Health Organization (WHO) (Geneva, Switzerland) estimates that 15 per cent of the world population consumes 91 per cent of the world's production of pharmaceuticals by value. The highly populated areas of the world, therefore, are characterized by a general lack of medicines. India, however, has a flourishing pharmaceutical and biopharmaceutical industry, providing lower-cost products, and is showing rapid development of biogenerics driven by an exceptionally well-qualified workforce.

The industrialized world will therefore need to meet a multitude of challenges from India and China, as these countries increase their significance as high-quality biopharmaceutical suppliers. In other parts of the world, such as North Africa, co-operative projects will help establish regionally adapted biological product manufacturing and supply. These challenging technology transfer initiatives are critical to help the developing world enter the knowledge-based era so familiar to the industrialized community.

References

[1] Innovation/Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products. March 2004 www.fda.gov/oc/initiatives/criticalpath

[2] Pharmaceutical cGMPs for the 21st Century – A Risk-Based Approach. September 2004 www.fda.gov/cder/gmp

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