Accelerated Product Development

Leveraging Industry and Regulator Knowledge to Bring Products to Patients Quickly

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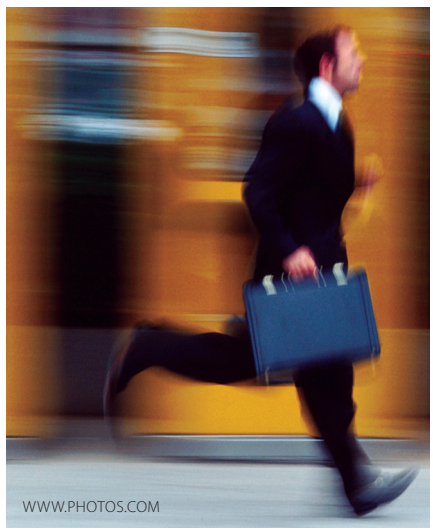
A Chemistry, Manufacturing and Controls (CMC) Strategy Forum titled "Accelerated Product Development: Leveraging Combined Industry and Regulator Knowledge to Bring Products to Patients More Quickly" was held in Washington, DC, on 27 January 2014. Biological therapeutics in development are demonstrating remarkable results in the clinic for many indications. So companies are seeking ways to accelerate the approval of these therapies and rapidly bring them to market.

Many such products take the form of well-characterized proteins (e.g., IgG1 or IgG2 monoclonal antibodies, MAbs) for which both industry and regulators can leverage extensive CMC and clinical experience. The need to reduce the time it takes to get biological medicines to patients for unmet medical needs, rare diseases, and orphan indications is a real concern. Even novel molecular entities such as antibody-drug conjugates (ADCs), bispecific proteins, and enhanced enzymes could use enhanced regulatory pathways to approval. Regulators have designed several pathways to accelerate the approval of such therapeutics, but the requirements for their CMC information packages are not always clear.



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This CMC Strategy Forum explored existing mechanisms for expedited approval, qualifications for expedited approval, and ways that industry and regulators can leverage existing knowledge to speed up product and process development as well as the marketing application process (e.g., through single-cycle formulation, computer modeling, and process characterization). The forum included discussion on assay development — especially for product-specific assays such as those measuring host-cell proteins (HCPs) and potency — and how it could be enhanced so that robust and sensitive assays for product characterization, lot release, and stability can be created quickly.

A critical issue for expedited approval of medically essential products is that sponsors may have limited (if any) full-scale batch experience, hence less registration stability and fewer batches to set realistic specifications. So our discussions touched on the best way to set meaningful specifications with little manufacturing experience and how a reasonable shelf-life could be set.

CMC Strategy Forum Series

The CMC Strategy Forum series provides a venue for biotechnology and biological product discussion. These meetings focus on relevant chemistry, manufacturing, and controls (CMC) issues throughout the lifecycle of such products and thereby foster collaborative technical and regulatory interaction. The Forum strives to share information with regulatory agencies to assist them in merging good scientific and regulatory practices. Outcomes of the Forum meetings are published in this peer-reviewed journal to help assure that biopharmaceutical products manufactured in a regulated environment will continue to be safe and efficacious. The CMC Strategy Forum is organized by CASSS, an International Separation Science Society (formerly the California Separation Science Society), and is supported by the US Food and Drug Administration (FDA).

Product Focus: Biologics

Who Should Read: Product development, business development, and regulatory affairs managers

Keywords: Market applications, EMA, FDA, Health Canada, prior knowledge, platform technologies

Level: Intermediate

Morning Session: Regulatory Requirements

The first session of the day was a workshop titled "Opportunities for Accelerating Biologics Program Development." This session explored different regulatory mechanisms available or under development in the United States and European Union for expediting product approval. In addition, we discussed the potential impact of such regulatory pathways on CMC development programs. Joseph Kutza (MedImmune) and Kimberly May (Merck) chaired the session.

Emanuela Lacana (US FDA Center for Drug Evaluation and Research, CDER) gave the first presentation: "Expedited Programs — Regulatory and Quality Implications for Product Development." Emily Shacter (ThinkFDA) presented the second: "Strategies and CMC Issues for the Development and Licensure of Breakthrough Protein Products." And Ilona Reischl (Austrian Federal Office for Safety in Health Care's Medicines and Medical Devices Agency) gave the third and final presentation: "Regulatory Experiences and Future Mechanisms to Accelerate Product Development and Approval in the EU." Reischl described current procedures for medicinal product approval in Europe and briefly summarized ongoing discussions regarding the conduct of clinical trials, transparency, and adaptive licensing.

A panel discussion concluded the morning session. Forum attendees were asked to point out aspects of the presented best practices — and the session overall — that needed further clarity. This panel discussion included Brendan Hughes (Bristol-Myers Squibb and Company), Emanuela Lacana (CDER), Helena Madden (Biogen Idec), Ilona Reischl, Anthony Ridgway (Health Canada), and Emily Shacter. The essence of this discussion is below.

Regulatory Mechanisms for Expedited Approval: The "US Pathways" box lists regulatory mechanisms for accelerated approval, priority review, fast-track, and breakthrough drug pathways. The "Canadian Pathways" box lists regulatory mechanisms for accelerated approval in Canada. And the "EU Pathways" box lists pathways for accelerated approval in the European Union.

The European Medicines Agency (EMA) recently launched an adaptive-licensing pilot project to improve timely access to new medicines for patients. This project explores an adaptive-licensing approach with real medicines in development. Sometimes called *staggered approval* or *progressive licensing*, this approach is part of the EMA's efforts to improve timely access for patients to new medicines. It is planned prospectively, starting with early authorization of a medicine in a restricted patient population. That is followed by iterative phases of evidence gathering, with later adaptation of the marketing authorization to expand access to the medicine for broader populations.

Analysis and Characterization: How can industry and regulators increase the pace of product and process development and marketing applications? Increasing the level of analytical characterization (e.g., single-cycle formulation, computer modeling, and process characterization) during early development can form a knowledge base required for the higher-level analysis of comparability to cover process changes when a minimal number of lots are produced during product and process development.

One question regarding products in an expedited program is whether sponsors should conduct more characterization than in "standard" product development because other areas of knowledge such as process understanding will be lacking. Using modern technology, industry should

Canadian Pathways

New Drug Submission (NDS)
Review is targeted within 300 calendar days.

A performance standard requires 90% of cost-recovered submissions to meet the review target.

Priority NDS
This shortens the review target to 180 days.

NDS with NOC/c (Notice of Compliance with Conditions)

Option can be requested in advance of market-application review based on promising clinical evidence.

An advance meeting allows the company and agency to agree on their path forward using this potential pathway.

US Pathways

Accelerated Approval
Surrogate endpoint reasonably likely to predict clinical benefit can be measured earlier than an effect on mortality or irreversible morbidity.

Process takes into account severity, rarity, or prevalence of the condition treated and availability or lack of alternative treatments.

Product must meet the same statutory standard for safety and effectiveness.

Sponsor must agree to conduct postmarketing confirmatory trials.

Priority Review
Drug treats a serious condition and, if approved, would provide significant improvement in safety and effectiveness.

The FDA evaluates every original application to determine whether it deserves priority-review designation.

Sponsors can request priority review.

The FDA may grant priority review within 60 days of submission.

This pathway shortens the review timeline from 10 months to six.

Fast Track
Drug treats a serious condition.

Product demonstrates potential to address an unmet medical need.

Expedited development and review involves frequent interactions with review team, potential priority review, and/or rolling review (Title IX, Section 901) (2).

Breakthrough Drug
Preliminary clinical evidence indicates that a drug may demonstrate substantial improvement over existing therapies based on one or more clinically significant endpoints.

Breakthrough-drug designation specifically instructs the FDA to expedite development and review of a drug or biologic (Title IX, Section 902) (2).

be capable of doing in-depth product characterization even at early stages of development.

Prior/Platform Knowledge: If a large amount of platform knowledge is available, then it should be leveraged and used to confirm data rather than build a data package from scratch. The burden of using prior/platform knowledge is in translating information from one molecule to another. Platform knowledge applies mainly to monoclonal antibody (MAb) products and may be easier for larger companies to use, with their experience from multiple products. Using such knowledge for accelerating programs requires a good understanding of expectations from the broader product development team — including clinical and commercial groups — to enhance information flow. That is critical in development of a rapidly moving CMC and clinical program. Informed decisions then can be made with regard to prioritization and timing.

Process Validation: Some industry representatives suggested rethinking process validation by leveraging life-cycle validation principles such as "continued verification" postmarketing, a focus on patient-safety attributes in validation protocols, and the use of cleaning verification rather than validation. Executing concurrent validation as more lots are produced could be possible because limited process understanding would have to be developed as each run is completed, allowing for continued verification over time.

That approach develops a validation protocol that will be agreed to in the marketing application, with data collected as batches are made after approval. At least one batch would be used for the application, with more batches added during review (and for preapproval inspections, PAIs) as well as later while the product is marketed. The protocol would include a process for dealing with aberrant lots. This concept is described for drugs in shortage and those manufactured infrequently (e.g., one lot a year, or even less) by the FDA's 2011 process validation guidance (**1**). Implementing it requires buy-in from compliance, field operations, and other stakeholders. They need confidence that a manufacturing process is under control (e.g., development and small-scale runs showing consistency), and a robust risk assessment is valuable. However, not all agencies have the mechanism for such a protocol; Health Canada, for one, does not.

From a control-strategy perspective, limited lots or process understanding could be amended by making commitments to enhance assay controls and reevaluate specifications after an agreed-upon number of lots have been manufactured or once sufficient knowledge is gained about both process and product. Thus, companies should focus on creating a reliable supply of high-quality product at market launch without the level of process optimization that often occurs during standard process development. That can be achieved, for example, by locking in a formulation and freezing cell-line development at phase 1, then launching from the clinical site to prevent any need for process/method transfer or requirement for associated changes. One participant suggested that it may not be wise to make wholesale changes during development (or immediately before commercialization). Instead, it might behoove sponsors to hold off until postapproval and when more process and product knowledge is gained, provided that the companies can meet and sustain market demand.

Bioassays: Design and validation of assays during product development is a challenge for accelerated-timeline projects. Bridging early fit-for-use assays with validated assays for process performance qualification (PPQ), validation, and postapproval is especially a concern. If a company can identify critical quality attributes (CQAs) as early as possible, it can then focus assay development on those product attributes most relevant to product safety and efficacy. Thus, the sponsor would need only to develop improved assays for attributes shown to be in control (e.g., process impurities or HCPs) or for noncritical attributes after licensure.

Having a potency assay is a statutory requirement, with regulatory expectations that it will be closely related to a drug substance's mechanism of action (MoA). Product sponsors should do their best to understand MoA even for expedited programs. Related data are often available from the earliest research stages and thus can be leveraged. Among the audience members, it seemed very rare to have a candidate in development without a presumed MoA. However, many sponsors have

European Pathways

Marketing Authorization (MA) Under Exceptional Circumstances

Comprehensive data cannot be provided.

Rare indications are treated.

Scientific knowledge is required.

Ethical issues are addressed.

Conditional MA

This features a less-complete data package, and approval is conditional.

Early evidence must suggest a positive benefit/risk determination.

Pathway is used when the patient population with a disease is small, and comprehensive clinical trials are not feasible — or if a medicinal product is intended to treat, prevent, or diagnose a seriously debilitating or life-threatening disease.

Compassionate Use

According to Article 83 of Regulation (EC) Nr. 726/2004 (**3**)

Pathway makes a product available to a group of patients with a chronically or seriously debilitating disease — or those whose disease is considered to be life threatening — and who cannot be treated satisfactorily by an authorized medicinal product. The product must either be the subject of a market-approval application (MAA) or ongoing clinical trials.

Named Patient Use

According to Article 5 of Directive 2001/83/EC (**4**)

This pathway is requested by an authorized healthcare professional for use by his or her individual patients under his or her direct personal responsibility.

found the development of reliable potency assays to be a potential rate-limiting step in product development. One potential mechanism to overcome that problem was use of increased numbers of replicates to decrease variability.

Risk Management: Overall, it is valuable to carry out risk assessments regarding the availability of less CMC information for a marketing application regarding patient benefit. This facilitates discussion of mitigation approaches with regulators. Neither industry nor regulators have enough transparency of risk-based decision making. It still appears that agencies are willing to make decisions only if full data packages are provided, even with prior knowledge available. If expedited approvals are to be successful in getting important medicines to patients earlier, then mechanisms need to be in place for reducing risk aversion among both industry and regulators.

Other Topics of Interest: In addition to the specific panel questions discussed above, the panel and audience then considered other aspects of expedited development programs, particularly for breakthrough therapies and later timing.

Lot Release for Breakthrough Therapies: When process characterization/development or complete validation are lacking during accelerated program development, lot-release testing could take on a larger role in assuring product quality. However, the old paradigm of "testing-in quality" is undesirable, and eventually it would necessitate good postmarketing planning and updates. Early limits are often broadly defined, so quality professionals need to look at actual data (rather than just specifications) and should judge in-process data and existing product knowledge when dispositioning a lot. Acceptability of specifications would be data-driven at the marketing-application stage.

One participant indicated that a regulatory agency should not be expected to play the quality system role for a breakthrough applicant. It is the product sponsor's responsibility to trend and analyze generated data, evaluate that information in the context of its specifications, maintain and present safety and efficacy information obtained during clinical trials, and propose corrective and preventive actions (CAPAs) if necessary.

Statutory Requirements for Approval and Compliance Involvement with Breakthrough Status: Despite the level of flexibility in CMC requirements described above (e.g., level of validation of assays and concepts of process validation), little flexibility should be found in the level of good manufacturing practice (GMP) requirements to assure product quality. However, some consideration of "phase-appropriate quality" allows GMP systems to be adapted as a product develops, with increasing stringency after market approval. To consider such an approach, a company might need deeper inspection a year or so after approval, but that depends on agency resources. Each product could get its own inspection risk assessment considering robustness of a company's quality system. The FDA's compliance branch should be consulted for determining the viability of such an approach.

Postapproval Challenges: If a comprehensive data package is lacking, then postmarket commitments can be a subject of dialogue with regulators both before and during market-application review. Should a program be approved based on phase 2 data, the possibility remains that rare adverse events could appear during broader phase 3 studies. However, that should be considered in a risk–benefit assessment and can be addressed partially through postmarket surveillance, such as through patient registries. Adverse events are generally associated with pharmacology of a drug rather than CMC issues (apart from immunogenicity associated with foreign sequences or protein aggregates, although in rare cases, contaminants may cause adverse reactions).

Companies also need to consider globalization of their products once they are on the market in one jurisdiction. Different regulatory regions may or may not have mechanisms for expedited approvals, but a solid CMC safety package is necessary regardless. Expedited applications still need data regarding viral clearance assessment and product characterization (e.g., fit-for-use assays). However, information gathered as lots are manufactured after the initial approval could be used to gradually increase the data package for other regions as necessary.

Breakthrough Designation Later in Development: Companies need to interact with regulators as soon as possible — when it becomes clear that a product's efficacy may warrant accelerated approval. This dialogue can cover what information is currently available, what would satisfy an expedited approval, and how to get there as quickly as possible. Obinutuzumab, marketed under the Gazyva name by Genentech (a member of the Roche family), was designated a breakthrough therapy later in development, when collaborative and rapid interactions between the company and regulators throughout the review period led to its expedited approval.

Afternoon Session: Platforms and Prior Knowledge

The second session of the day was titled, "Leveraging Prior Knowledge and Platforms to Expedite Development for Accelerated Clinical Programs," chaired by Michelle Frazier (Amgen Inc.) and Emily Shacter (ThinkFDA). In the first talk, Earl Dye (Genentech, a member of the Roche Group) addressed "CMC/GMP Considerations for Accelerated Development and Launch of Breakthrough Therapy Products." He described how accelerated clinical-development timelines for breakthrough products necessitate a different approach to product and process development, and to commercial readiness. It requires front-loading certain development activities to ensure a reliable supply of product at market launch. Leveraging prior knowledge and platform data, implementing comparability protocols, and making flexible manufacturing

arrangements for potential launch from a clinical-material facility are key considerations for success. Dye also described accelerated manufacturing and launch scenarios for large-molecule breakthrough therapies, and he listed activities that may be negotiated with FDA for deferring to the postapproval period without compromising patient safety

In the second talk of the session, Stephan Krause (MedImmune) presented "Risk-Based Strategies for Analytical Method Qualification/ Validation Studies to Support Accelerated Product Development." He emphasized ensuring the accuracy and reliability of analytical methods throughout a product's life cycle. Strategies he presented are intended to minimize the risk of potential delays in product development or approval. Krause covered risk-based concepts and gave examples illustrating how analytical methods can be qualified, transferred, and validated based on type, intended use, and/or prior experience (e.g., analytical platform technologies) to support accelerated product development and process validation studies. He went on to describe how opportunities exist for reducing typical analytical method lifecycle steps in accelerated development programs using (analytical) platform technologies. In addition, reducing analytical method lifecycle steps can occur during later-stage development (before process validation starts) while keeping risk(s) mostly to manufacturers rather than patients.

Finally, Nancy Green (Health Canada) discussed, "Leveraging Health Canada's Regulatory Framework to Accommodate Accelerated Product Development for Biologic Drugs." She covered Canada's Food and Drug Regulations, which are considerably flexible regarding what constitutes satisfactory evidence of safety, efficacy, and quality for a new drug. Green represented Health Canada's Biologics and Genetic Therapies Directorate (BGTD), which uses that flexibility to create a multifaceted quality review approach with dossier review, on-site-evaluation, and a lot-release program that covers both premarket and postmarket products. Depending on the situation, more or less emphasis can be placed on certain elements to obtain satisfactory evidence of safety and quality for a product under review. The BGTD quality groups take a life-cycle approach: The same group reviews a product from clinical-trial applications through new drug submissions to postmarket submissions. Review teams tailor their strategy to each submission. Especially if accelerated product development is anticipated, early and ongoing meaningful discussions between reviewers and sponsors regarding the strengths and weaknesses of the approach (and associated data) are critical for success.

A panel discussion followed those presentations. This questions-and-answers session was conducted by Rohini Deshpande (Amgen Inc.), Earl Dye, Chana Fuchs (CDER), Nancy Green, and Stephan Krause. After specific panel questions (detailed below), a general discussion followed.

How can process development be structured so that material can get to patients in a shortened timeframe? Use of platform knowledge should help speed up process development by creating a single-cycle development program (with no need to redevelop a process for commercial manufacturing after clinical production). Although such an approach could work for platform products (e.g., MAbs), it may be unlikely to work with nonplatform molecules. Companies can consider drug product as well: focusing on the final product formulation/delivery presentation from the start (e.g., prefilled syringe). But perhaps a simple presentation (e.g., in a vial) would be the quickest approach to product launch.

Molecular modeling (screening and altering sequences for improved stability, lower viscosity, a better immunogenicity profile, and so on) can be used to determine protein sequences and screen for the best development candidates. This can speed up process development if difficult quality attributes (e.g., aggregation and oxidation) that usually need to be controlled by process operations can be screened out before development begins.

One industry representative suggested that dual-cycle cell line development can move material to patients earlier. That approach would be based on an early cell line, with material produced from pools for toxicology and early phase clinical studies, deferring cloning until after trials are successful. As described above, using one lot for all early clinical studies eliminates comparability concerns based on product understanding because there are no process changes. However, this strategy dramatically increases the work needed to characterize a product once its program moves ahead and more lots are made with a cloned cell line.

How can assay development be enhanced to create robust and sensitive methods for product characterization, lot release, and stability testing in a shorter timeframe? Applying platform knowledge is also valuable in assay development. Using platform methods here reduces concomitant qualification needs.

INTERACTION
and communication between industry and regulators during accelerated programs should improve their chances of success.

Validation of analytical methods can be balanced with method qualification depending on the criticality of each attribute tested and the material involved (whether product, in process pool, raw material, or so on). Novel approaches to "open" validation protocols can be assessed by which a method is validated as more data come in (e.g., as sensitivity and robustness data accrues over time). Keeping all testing at one site throughout development and marketing eliminates the need for process transfer, which in itself can reduce the need for highly robust assays.

What is the best way to set meaningful specifications with very

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Siddharth J. Advant (Kemwell BioPharma), John Dougherty (Eli Lilly and Company), Christopher Joneckis (CBER, FDA), Junichi Koga (Daiichi Sankyo Co., Ltd.), Steven Kozlowski (OBP, CDER, FDA), Rohin Mhatre (Biogen Idec Inc.), Anthony Mire-Sluis (Amgen, Inc.), Wassim Nashabeh (Genentech, a Member of the Roche Group), Ilona Reischl (BASG/AGES, Austria), Anthony Ridgway (Health Canada), Nadine Ritter (Global Biotech Experts, LLC); Mark Schenerman (MedImmune), Thomas Schreitmueller (F. Hoffmann–La Roche, Ltd.), Karin Sewerin (BioTech Development AB)

little manufacturing experience? For medically essential expedited product approvals, sponsors may have such limited (if any) full-scale batch experience. The panel suggested several approaches:

- Leverage all product and process data when setting specifications, including prior knowledge.
- Consider broader product quality acceptance ranges for noncritical quality attributes until further process knowledge is gained after market approval.
- Set broader specification limits in the market application, and propose to update those after product approval.
- Include a larger number of tests in the market application, and justify reduced testing after product approval.

How can a reasonable shelf life be set for an expedited product? Appropriate expiry dating can be achieved by understanding degradation pathways early on, with stability-indicating assays based on platform knowledge. That focuses on only those quality attributes that exhibit meaningful degradation over time. One industry representative suggested that with such focused use of accelerated and forced-degradation studies — as well as predictive models (for small and large molecules) — an assurance level is possible for stability beyond real time at recommended storage. It is also feasible to launch a product with reduced real-time stability data for commercial material and leverage more extensive stability data from development lots. But product comparability also must be considered in such cases: Those development lots must be shown to be comparable to commercial lots. Increasing the testing frequency for stability programs during development allows more data points to be gathered and provides statistical assurance for protocols with much longer intervals (thus providing more data for limited batches being produced).

During creation of a marketing application, a company can develop its postapproval stability extension protocol for submission. Sponsors can submit with limited real-time stability data and more forced-degradation/stressed stability data in their applications and then update those during review. However, that assumes that an agreement with the review team can be gained for this approach before submission. It can be discussed at meetings generally held before compilation and submission of biologics license applications (BLAs).

Where else in CMC development can industry work with regulators to speed new products to market (e.g., stability requirements, potency assays, GMP inspections)? As described above, a more flexible approach to stability would be very helpful. It could allow for use of real-time expiry extensions based on earlier lots, molecular modeling, and demonstrated comparability of lots used to support stability. Companies need a phase-appropriate/accelerated development approach for quality systems, validation, and so on that both meets GMP requirements and allows for flexibility to facilitate rapid development at early stages. For example, the change control and deviation systems could be different at early clinical phases from those used at commercialization.

Increased interaction and communication between industry and regulators during accelerated programs should improve their chances of success, reduce mistakes and questions, and thus shorten the path to approval. Close collaboration also can force sponsors to think about innovative approaches (e.g., continuous manufacturing or process analytical technology, PAT), and discussions with reviewers are essential if those are to be adopted. Discussions are ongoing within various agencies to address increasing timeline expectations. Regulators are looking at bottlenecks to find ways to improve review processes across the board (e.g., through cross training or cross-division review). Allowing crossjurisdiction agency discussion could help, but that would need to be approved by a product sponsor.

Approving supply chain aspects such as new manufacturing or distribution sites, second-source raw materials, and so on for postapproval consideration with a breakthrough drug could also accelerate timeframes to ensure timely accessibility of material to patients. Sponsors can discuss such aspects with regulators to speed up application review, with protocols or other tools used in advance. Involving the same review team that reviewed the marketing application would help move things along. In addition, existing guidance on preventing drug shortages can help companies develop their own robust supply chains, even for accelerated products. The consensus was that an overall movement (with regulatory agency adoption of risk-based approaches and reduced risk aversion) would have to occur for expedited approvals of critical medicines to occur more generally.

Other Topics Addressed: In addition to the specific panel questions above, the audience and panel members continued to discuss some other aspects of expedited development programs, including product pools, diagnostics, and postmarket planning.

Production Cell-Line Pools: If no detrimental effect on safety occurs, the use of a pool-derived cell line to manufacture toxicology and clinical-testing material should be a viable proposal to allow for more rapid screening of potential therapeutic candidates in early development. As always, data will drive acceptability. Controlling product quality variability is critical. Analytics must be in place to ensure that a product is appropriately

characterized and its manufacturing process is well controlled.

Showing product comparability with a cloned cell bank will be essential in further stages of development. From a safety and cell characterization perspective, a cell bank derived from pools would be treated the same way as a cloned cell bank, but companies need to do more for product characterization to assure product consistency, because a pooled cell bank isn't clonal. Some potential regulatory questions need addressing before this approach can be implemented: specification and characterization testing strategies, analytical assays for low-level detection of microhetereogeneity (variants and impurities), and comparability assurance when bridging early material with late-phase material.

One participant raised the theoretical possibility that dilution of product variants/impurities could go undetected and that use of a nonclonal cell line could cause safety concerns — making toxicological studies important. Others highlighted that although a cell-line change during development is a common practice, use of pools to make early material for human studies is a new concept. So sponsors would need to provide justification and data to regulatory authorities to advance the approach. When using cell banks derived from pools, a company has to consider what is carried out when moving from the pool to the cloned cell-line material. Is repeated preclinical/pharmacokinetic testing necessary, or would analytical characterization suffice? Using an in-depth comparability study should not require such testing to be executed before pivotal clinical studies commence.

When using the pooled–cell-line approach, a company needs to determine how to select which pools to use. Current strategies focus on the median attribute profile of product produced. A pooled–cell-line approach could take a product through phase 1 with a mixture of attributes that provide "coverage" for when a cell line is finally cloned. But that is not the aim for pool cloning; it is rather to make product that is less variable from a microheterogeneity standpoint at the outset.

Diagnostics: Once a need for a diagnostic is identified, regulators will need to mediate intercenter discussions when the Center for Devices and Radiological Health gets involved. Biopharmaceutical companies often outsource diagnostic development or enter into licensing and comarketing agreements with diagnostic companies, both of which also would need coordinating discussions with regulators ahead of time. Medical device guidance for diagnostics is very different from that associated with biologic/drug development. So any company that will require development of a companion diagnostic (regardless of development timelines) must be aware of such regulations to prevent delays in approval.

Postmarketing Plans in Marketing Application Filings: One of the most valuable tools to use when creating a marketing application for expedited approval is inclusion of postmarketing plans and protocols. They can be used later to execute postmarketing changes to a control strategy, to make stability-related extensions to shelf-life specifications, and to scale up or move manufacturing to other facilities. To identify gaps and mitigated postmarketing problems in advance, such plans and protocols often require trusting and open discussion between a company and its regulatory reviewers. Quality system robustness is also essential to ensuring success. Approval timelines could be delayed if an agency is not convinced that a company's quality system will identify excursions to agreed-upon protocols or that appropriate mitigations would be put in place by that company.

References

1 CBER/CDER/CVM. *Guidance for Industry: Process Validation — General Principles and Practices.* US Food and Drug Administration: Rockville, MD, January 2011; www.fda.gov/downloads/Drugs/Guidances/UCM070336.pdf.

2 112th Congress. *Public Law 112–144: FDA Safety and Innovation Act of 2012.* US Government Printing Office: Washington, DC, 9 July 2012; www.gpo.gov/fdsys/pkg/PLAW-112publ144/pdf/PLAW-112publ144.pdf.

3 Article 83 of Regulation (EC) Nr. 726/2004; *Off. J. Europ. Union* 30 April 2004: 1–33; www.biosafety.be/EMEA/726_2004_EN.pdf.

4 Article 5 of Directive 2001/83/EC. Off. *J. Europ. Union* 28 November 2004: 67–128; www.edctp.org/fileadmin/documents/ethics/DIRECTIVE_200183EC_OF_THE_EUROPEAN_PARLIAMENT.pdf.

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