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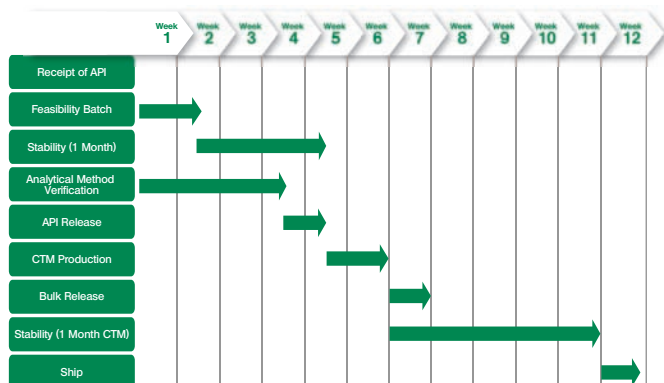


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Illustration by Dan Ward
Images: Maria Toutoudaki/Getty Images

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Correction:

In the March 2015 issue article, "Implementation of ICH Q3D Elemental Impurities Guideline: Challenges and Opportunities," the term "arsenic" was incorrectly used in place of "antimony." The correct statement is:

While certain materials were found to contain elemental impurities, the presence of the elemental impurity was predominantly associated with deliberate use of metal catalysts, for example the use of antimony in the manufacture of polyethylene terephthalate (PET).

The corrected article can be found on www.PharmTech.com.

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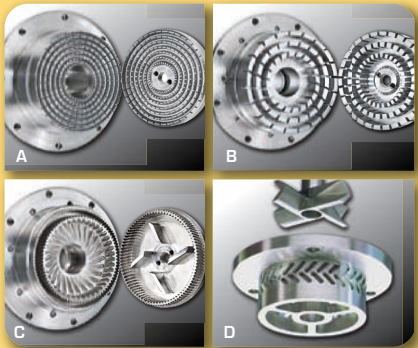
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Welcome to the Biosimilar Era

Rita Peters

FDA approves a biosimilar and loses a commissioner in March.

Approvals of most generic drugs receive little fanfare. FDA's approval of the first US biosimilar product—Zarxio (filgrastim-sndz) from Sandoz—in March, however, garnered a wealth of media and public attention. A biosimilar to Amgen's Neupogen (filgrastim), which was originally licensed in 1991, Zarxio is approved for the same indications as Neupogen and may be prescribed by a healthcare provider for patients undergoing cancer treatments or those with neutropenia. The approval of the first biosimilar comes five years after the enabling legislation, the Biologics Price Competition and Innovation Act of 2009, was passed as part of the Affordable Care Act that was signed into law in March 2010.

Janet Woodcock, director of the Center for Drug Evaluation and Research described the Zarxio approval as “a significant milestone in FDA's regulatory history” (1). She noted that the initial approval paved the way for future biosimilar approvals, and a successful review process could provide more affordable treatments to patients and spur development of a new segment of the biotechnology industry.



Rita Peters is editorial director of *Pharmaceutical Technology*. Send your thoughts and story ideas to rpeters@advanstar.com.

Slow path to milestone

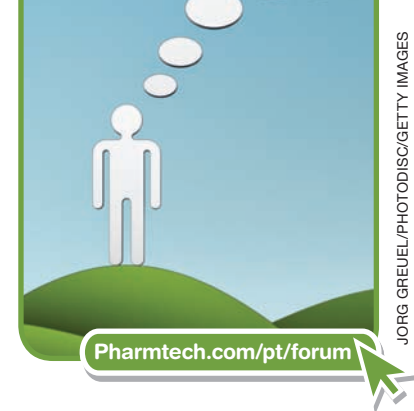
The approval marked a turning point for the biopharmaceutical industry; however, it also is an indicator of how the United States lags the rest of the world in biosimilar development and use. Regulatory pathways for biosimi-

Questions about the development and acceptance of biosimilar drugs remain.

lar approval have been established in other parts of the world for some time. The Zarxio approval comes nearly a decade after the first biosimilar drug was approved in Europe; in fact, biosimilar filgrastim is available in more than 60 countries worldwide.

Questions about the development and acceptance of biosimilar drugs remain:

- On the patient level, the decision to switch from a branded biologic to a biosimilar is up to the prescriber; however, the potential for immunogenicity due to the change in biologic product is a concern.
- Analytical studies to evaluate similarity can be challenging and applications must have sufficient analytical data.
- The naming convention for biosimilar products is a hot topic for manufacturers and healthcare



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providers. While FDA works on draft guidance for the naming of biosimilars, a placeholder nonproprietary name—filgrastim-sndz—is used to identify the product. A guidance document for biosimilar labeling is also in the works.

While Sandoz has a green light from FDA to move forward with Zarxio, pending legal action threatened to delay the market release in early April.

Change in FDA leadership

While March marked a new beginning for FDA with the biosimilar approval, it also marked the end of the six-year tenure of Margaret Hamburg as FDA commissioner.

When Hamburg announced that she was stepping down in February, the news generally was met with praise for FDA accomplishments during her tenure including an increased emphasis on science-based regulation, efforts to streamline product approvals, and addressing challenges of operating in a globalized drug market.

Addressing the unresolved and unknown challenges in the biosimilar era—along with many other issues facing the agency—will be left to the next FDA commissioner.

I would like to thank Dr. Hamburg for her service and urge the President and Senate to act swiftly to appoint and approve a successor.

Reference

1. J. Woodcock, CDER Center Director e-mail, March 6, 2015. **PT**

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Modern Manufacturing Systems Key to FDA Quality Initiative

More reliable operations would accelerate product development and prevent drug shortages.

To ensure patient access to high quality, safe, and effective medicines, FDA spends considerable time and resources enforcing GMPs, inspecting production facilities, and overseeing a growing volume of imported pharmaceutical ingredients. Agency officials have urged biopharmaceutical manufacturers for more than a decade to adopt more reliable and efficient advanced manufacturing technologies capable of ensuring consistent high-quality production that meets standards and public expectations. Such approaches, the authorities predict, could reduce waste, prevent drug shortages, and avoid the scale-up and production challenges that can delay final approval of innovative breakthrough therapies.

Agreement on metrics has been tricky.

To support real change, FDA's Center for Drug Evaluation and Research (CDER) has launched a full-court press to convince industry of the value of adopting modern drug manufacturing systems. The agency seeks clearer standards and policies that provide more predictability and reduced oversight of firms that invest in more efficient production methods. At the same time, more transparent company reports on quality operations, market pressures to cut costs, and public demands for reliable patient access to critical therapies are combining to support a shift away from outdated, unreliable production methods.

CDER's new Office of Pharmaceutical Quality (OPQ), led by CDER director Janet Woodcock, is establishing systems to identify high-risk, problematic facilities and products—and those operations that reliably achieve quality standards—to be able to detect and respond to quality issues before they disrupt production and lead to plant closures. Woodcock has repeatedly called for industry investment in advanced manufacturing systems as part of her vision for shifting from rule-based to risk-based regulation, offering less oversight of operations and products that demonstrate a capacity to ensure quality and reduce risk. She reiterated this approach at the February 2015 annual meeting of the Generic Pharmaceutical Association, urging development of continuous manufacturing operations that can achieve consistent product quality.

Quality data key

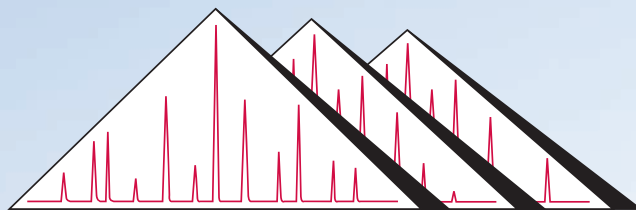
Science-based standards for application review and plant inspection support this approach by communicating clear expectations for industry. Such standards will aim to capture critical product attributes that can indicate quality problems, needed corrective actions, and justify enforcement decisions. OPQ's Office of Policy for Pharmaceutical Quality (OPPQ) is examining current policies and areas where risk-based regulation and guidance would encourage continuous quality improvement by industry throughout drug development and production. OPPQ further coordinates FDA quality-related policies with other regulatory authorities and with independent standards-setting organizations.

This approach will be supported by a new quality metrics reporting initiative that requires biopharma companies to submit data on operations key to consistent quality production. FDA has been working closely with industry for more than a year to devise a set of metrics that will indicate the ability of a firm and its facilities to produce high-quality therapies on a continual, error-free basis. Likely measures include right-first-time rate, quality-related complaints, invalidated out-of-specification results, recalls, and stability failures.

Agreement on metrics has been tricky, though, as seen in delays in publishing draft guidance on which production measures may be most accessible and useful. Discussion has been most intense on devising a set of metrics that indicate the "quality culture" at a company (1).

Industry metrics will be part of a comprehensive information system that will manage the "inventory" of CDER-regulated manufacturing sites and products. This information technology system is being developed by OPQ's Office of Surveillance to track the state of quality for all regulated sites based on data from applications, inspections, and quality metrics reports. A risk-ranking process for all locations will drive CDER inspection planning and site visits, with an eye to focusing on more serious problems. Metrics may inform inspection frequency, help FDA set inspection priorities, and identify products and processes to target (or omit) during a site visit.

Ideally, the program will identify and reward firms that "go above and beyond" meeting basic standards, preferably by investing in modern, continuous manufacturing systems and high-tech processes that ensure quality production. "Quality scorecards" devised by OPQ would inform companies confidentially on how they compare to industry performance.



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While CDER does not plan to publish specific company ratings at this time, a manufacturer could choose to promote high quality reports to payers, patients, and health professionals.

Biopharma companies that take steps to enhance manufacturing quality should be better positioned to expedite development and production of innovative therapies promising important benefits for patients with critical illnesses. OPQ's lifecycle review initiative and its team approach for integrating quality review and compliance aim to support accelerated review of a growing cadre of breakthrough drugs.

Changes in OPQ's Office of Biotechnology Products (OBP), for example, aim to enhance its capacity for assessing the quality and safety of a broader range of biotech therapies in development or under review by the agency, including orphan drugs and biosimilars that raise new analytical challenges. OBP now has four Divisions of Biotechnology Product Review & Research, each with a cadre of reviewers and scientists capable of assessing a spectrum of biotech therapies. This structure replaces specific divisions for monoclonal antibodies and for other proteins staffed by more specialized reviewers. The change should help OBP manage its workload more effectively as biotech product development continues to expand, OBP chief Steve Kozlowski explained at the January 2015 WCBP symposium in Washington, D.C. (2).

Reducing shortages

More information on the ability of a production facility to consistently produce high quality products also can help FDA identify potential problems early on that could cause manufacturing disruptions or failures in product quality. Such situations often result in critical drug shortages, particularly for low-cost sterile injectable products made by a limited number of generic-drug companies. FDA has been able to prevent and mitigate drug shortages more often in the past two years by obtaining earlier reports from manufacturers of potential production problems or ingredient shortages (3). But a more long-term solution lies in industry investment in advanced manufacturing systems and adoption of a quality culture in their operating units that encourage employee creativity and proactive risk management.

Such an approach is described in a new technical report from the Parenteral Drug Association (PDA) on how manufacturers should establish a risk-based approach for preventing and managing drug shortages (4). The report outlines a model for companies to assess the factors likely to lead to a shortage and its potential impact on patients. For certain high-risk situations, a manufacturer should consider adding manufacturing sites or lines, engaging additional raw material suppliers, and installing new equipment and technology.

The prospect of more transparency in company quality performance may drive such change, as will pressure on manufacturers to achieve more efficient and economical production systems to cut costs in response to squeezed revenues from more price-sensitive customers. Regulatory carrots and sticks have provided some incentives for industry to replace outdated facilities, but the market shift from blockbuster drugs for chronic conditions to "precision" medicines for small patient populations should do much to further investment in more flexible and cost-effective operations.

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The Role of Regulatory Advice in Drug Development

Drug developers understand the importance of early communication with regulators, but is EMA providing enough flexibility and support to companies?

Regulators are helping to drive a surge in the development of innovative medicines and their manufacturing processes in Europe by giving advice and encouragement to companies, particularly the small and medium-sized enterprises (SMEs). The support has been especially effective in helping to achieve a big increase in the development of medicines for treating rare diseases. Nonetheless, companies, patients groups, and healthcare professionals believe that regulatory agencies could do more to assist small innovators, especially in the creation of new production processes. Regulators, as well as drug producers themselves, are also being criticized for not doing enough to tackle the relatively high rate of shortages of medicines for rare diseases, often caused by manufacturing disruptions.

National agencies in Europe are running advisory services to assist companies in the development of new medicines and processes.

SMEs are now making more use of the various initiatives that the European Medicines Agency (EMA) has introduced to help them develop new medicines. In the four years leading up to 2014, 64% of SMEs working on new medicines requested scientific advice from EMA on their drug development compared with 40% in the previous four years, according to the agency's annual SME report (1). This rise was accompanied by a jump in the proportion of successful applications by SMEs for marketing authorizations, from 49% in 2007–2010 to 62% in 2011–2014.

At the same time, involvement of drug developers and drug producers in the process for orphan medicine approvals, many of them developed by SMEs, is growing rapidly. The number of applications for orphan product designation rose 63% in 2014 to 327 applications compared with 2013, according to figures from the EMA's committee for orphan medicinal products (COMP) (2). This figure was more than three times higher than 10 years ago. Allocations of orphan medicine designations went up 18% to 160, while those actually gaining marketing authorizations rose 71% to 12 (2).

Advanced therapy medicinal products

There is also a rising number of leading edge innovations categorized as advanced therapy medicinal products (ATMPs), made from tissues, genes, or cells, which may offer groundbreaking new treatment opportunities for many conditions. EMA's committee for advanced therapies (CAT) has issued more than 100 recommendations for the classification of innovative medicines as ATMPs (3). Of new medicines under development for the treatment of rare diseases or that are categorized as ATMPs, micro-, small-, or medium-sized companies account for half, according to EMA (1). Yet, while SMEs are becoming major drivers behind medicine innovation in Europe, they are still struggling to gain authorizations, at least at the level of centralized approvals. The number of orphan medicine approvals has actually been decreasing as a proportion of designations. On the basis of COMP's statistics, the proportion of approvals to designations was 5.6% in the five years prior to 2014 compared with 9.2% in the previous five years (2).

"The development of orphan medicinal products remains a risky undertaking for those investing in the research, development, and commercialization of these treatments," says Miriam Gargesi, director of healthcare biotechnology at the European Association of Bio-Industries (EuropaBio), Brussels. "Due to the rarity of the diseases, there is often only partial knowledge of the mechanisms of the diseases, scarce medical expertise, and recruitment for clinical trials is a challenge."

Advisory services

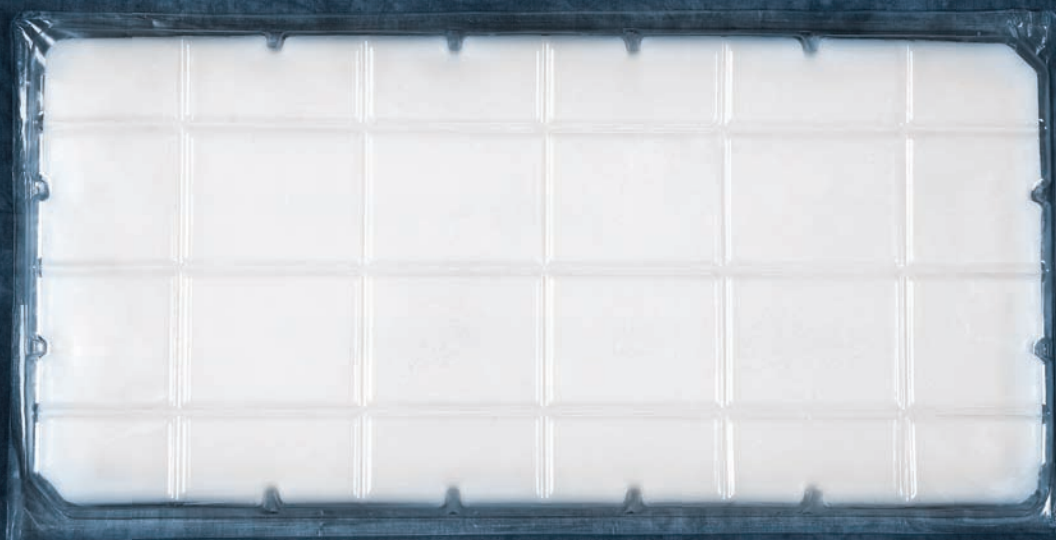
In addition to EMA, national agencies in Europe are running advisory services to assist companies in the development of new medicines and processes. Large companies and SMEs are being encouraged by their national authorities to contact them as early as possible in the development of medicines to ensure that their manufacturing processes will not create regulatory obstacles, which could be expensive to overcome.

The United Kingdom's Medicine and Healthcare Products Regulatory Agency (MHRA) in London has published a series of case studies describing the assistance it has been giving to companies in the process development and preclinical stage of medicine innovation. For example, the agency has been advising OxSonic, Oxford, England, a spin-off from Oxford University, on the quality assessment and controls of particles for use in a technology for the enhanced delivery of anti-cancer drugs deep into solid tumors. Within the university itself, the MHRA has also

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been helping the Jenner Institute and the university's clinical biomanufacturing facility in the development and production of a new malaria vaccine through the bio-engineering of a viral vector.

The agency has also been giving guidance to companies in the design of new sites and plants, sometimes even prior to an investment decision. One of these investments has been a £120 million (\$184 million) plant at Macclesfield, northeast England, in which AstraZeneca is making a sterile implant for treating cancer, involving multiple aseptic stages.

"It was essential that we had a good understanding of the regulatory expectations very early on in the process to understand the impact on the design, cost, and time lines in proposing the business case for the Macclesfield location," explains John Parker, AstraZeneca's UK quality director.

Quality issues

Much of the advice being offered by EMA and national agencies is focused on helping companies, particularly SMEs, to prepare their medicines properly for clinical trials where most new products fail. But for a large proportion of producers, quality issues, often linked to the manufacturing process, are a major issue.

In dossiers for marketing authorization applications by SMEs in 2011–2013, 46% of major objections by regulators were related to quality issues compared with 47% that were because of clinical efficacy and safety matters, according to an EMA investigation, the results of which are published in its SME annual report (1). Of applications for biologics, 51% of objections were on quality topics while for chemical entities, it was 41%.

Among the most frequent problem areas was the quality documentation related to manufacturing process validation, said the EMA report (1). Other issues included control and/or characterization data of the active substance or the finished product, stability, compatibility, and shelf life data and pharmaceutical development.

A joint study (4) published by the Deerfield Institute, the research arm of the Deerfield investment organization, and EuropaBio, found that SMEs welcomed regulatory scientific advice because it provided "opportunities to get input on manufacturing processes, [which was] particularly important for complex products that involve newer technologies, such as genetic engineering." The companies, however, complained about a lack of flexibility among the agencies, particularly EMA, according to the report which was based on interviews with companies, regulators, and reimbursement authorities.

EMA, for example, wanted specific rather than open questions, making it difficult for companies to work out what would be the right questions. Compared with the advice from local agencies, "the EMA process can be lengthy, formal, and cumbersome," the report said. Apart from informal exchanges in pre-submission meetings, "there are not enough opportunities for discussion with EMA reviewers," the report added.

Mitigating drug shortages

SMEs and larger companies have been criticized for not doing enough to ensure the reliability of their production processes once they start making commercial quantities of their medicines. This is especially the case with treatments for rare diseases, for which there have been a disproportionate level of shortages caused often by manufacturing failures. A group of European healthcare NGOs, led by EURORDIS, a rare diseases patients group, has argued that the incidence of drug scarcities has become so serious that supply shortage risk assessment plans should be provided by manufacturers before their medicines are granted marketing authorizations.

"The current risk management plans submitted by marketing authorization applicants do not contain information on risks related to manufacturing issues or shortages as this is not legally required," explains Francois Houyez, EURORDIS' health policy advisor. "Applicants could submit information on these aspects on a voluntary basis, but to make it mandatory would require legal changes."

Some companies argue that the solution to shortages could be more thorough GMP inspections. "We question whether more inspections would help and regulators don't seem to think so either," says Houyez. "Thinking that more inspections would reduce the risks of shortages, even with an army of inspectors worldwide, is not the way forward."

EMA believes that the industry should be more pro-active in the assessment and management of the risks of shortages not only at the production stage but throughout the supply chain. Industry associations have a role to play in the promotion of information sharing and the development and sharing of the methodologies for risk assessments, Brendan Cruddy, EMA's head of manufacturing and compliance, told a rare diseases conference in Berlin in 2014 (5). "Industry, don't compete. Collaborate," said Carla Hollak, a professor in metabolic diseases at Amsterdam University's Academic Medical Centre, at the same meeting. The development of innovative medicines and production processes is becoming dependent not only on guidance from the regulators at an early stage, but the industry also needs to work more closely together to ensure the efficiencies of their supply chains.

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EMERGING MARKET REPORT



Drug Discovery and Development in: **India**

Jane Wan

Hope abounds for local drug discovery companies despite challenges at home.

Indian pharmaceutical companies' entry into the drug discovery and development field dates back to the early 1990s when India announced the signing of the World Trade Organization (WTO) agreement that introduced a product patent system from Jan. 1, 2005. Changes in the regulatory environment in the same year led to other developments with the emergence of the country as a favorite destination for "chemistry" outsourcing followed by "collaborative drug discovery as contract agencies where in-house strengths in chemistry of local companies was augmented with focus biology" (1).

Over the past few years, Indian pharmaceutical companies have been attempting to re-orientate their efforts toward developing new innovative medicines, Ang Wei Zheng, analyst of Business Monitor International (BMI) says. However, BMI maintains that the transition by Indian generic-drug makers will remain slow given the high risk levels associated with drug discovery.

Despite this, local companies made headway in this sector. In May 2012, Ranbaxy Laboratories launched Synriam (arterolane maleate plus piperazine phosphate), a new drug for the treatment of uncomplicated Plasmodium falciparum malaria. Similarly, Cadila Healthcare launched Lipaglyn (saroglitazar) in June 2013, for the treatment of diabetes. Saroglitazar is claimed to be the first new chemical entity (NCE) discovered and developed by an Indian pharmaceutical company.

Local companies in drug discovery

Recently, Indian companies such as Bugworks in Bengaluru and Vitas Pharma in Hyderabad have ventured into drug discovery. Ang says, "The move of Indian start-ups into the drug discovery space will present a new source of innovative medicines to the Indian pharmaceutical sector. However, we expect their impact to come primarily through collaborations."

The Indian business environment will remain highly challenging for start-ups due to low levels of intellectual property protection, pricing uncertainties, and delays in receiving clinical trial approvals. In addition, venture capital and private equity have not been

actively supporting such biopharmaceutical start-ups, leaving such companies to turn towards larger multinational pharmaceutical companies and domestic drug manufacturers for funding, he adds. According to a study into life-sciences venture capital published in 2013, only 32 out of a surveyed 170 biotechnology firms in India were backed by venture capital (2).

Market challenges

Pharmaceutical companies operating in India face distinct challenges. Arvind Pachhapur, country head, intellectual property and science and legal business of India Thomson Reuters says, "They include insufficient innovation, limited access to high risk funding, short supply of skilled professionals, and specialized equipment."

Low levels of intellectual protection continue to be a problem, Ang says. India registers a low score on BMI's Pharmaceutical Risk/Reward Index (RRI)'s measure of Patent Respect (an index providing a globally comparative and numerically based assessment of a market's attractiveness for innovative drug makers) compared to its Asian counterparts such as China and Indonesia (3). The low score is driven by the frequent threats to patents through compulsory licenses being revoked or rejected by the patent office.

Pachhapur says, "The clinical-trial segment also faces challenges such as regulatory uncertainty regarding conduct of trials, unethical practices, and approval delays." It is estimated that it takes one year in India to gain regulatory approval of trials as compared with just 28 days in the United States. This is further compounded by regulatory uncertainty following the US Supreme Court's ruling in 2013 to suspend 157 previously approved clinical trials, Ang adds.

As a result, Indian pharmaceutical companies have begun to move their operations outside of the country, despite the potentially higher cost. Lupin Pharmaceuticals has set up two research and development plants in the United States while Cipla said in July 2014 that it will invest \$150 million in the United Kingdom for research and clinical trials. Clinical trials in India declined from 264 in 2009 to 174 by 2013, according to ClinicalTrials.gov (4).

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REGULATION & COMPLIANCE

India's pricing regulation continues to undergo significant changes that create high levels of uncertainty in launching new drugs, Ang says. In September 2014, the government rescinded guidelines issued the previous May that would have given the National Pharmaceutical Pricing Authority (NPPA) the power to set prices of non-essential medicines. In December 2014, however, the NPPA announced that it will bring an additional 52 new drugs under price control. Consequently, drug makers have cut back on the number of medicines launched; data from the Central Drugs Standard Control Organization highlights a decline from 270 in 2008 to 56 as of November 2014.

Market opportunities

Despite these challenges, industry players can still explore opportunities in the local business environment. Driving these prospects includes the country epidemiological transition with the burden of non-communicable diseases growing while the burden of communicable disease continues to decline, according to BMI's Burden of Disease Database (BoDD) (5). In addition, drug-discovery companies in India are supported by a large pool of human resources with 14% of graduates in 2012 coming from science-related backgrounds. Furthermore, tertiary education remains strong, which drives the country's score of 73.6 on BMI's Operational Risk's measure of Tertiary Education—above the Asia Pacific's average (6).

Government initiatives

According to Pachhapur, the government has taken many initiatives in accordance with India's Department of Pharmaceuticals Pharma Vision 2020 (7), which is designed to make India a hub for end-to-end drug manufacturing. He says, "To encourage greater participation from industry players, the government may want to consider dialog and collaboration between the government policy makers, senior leadership of Indian pharmaceutical industry and key opinion leaders from research institutes and academia on ways to better support novel drug discovery in India. The regulatory guidelines should be amended to encourage global pharmaceutical companies to not only continue outsourcing their research and development activities to Indian companies but also work on end-to-end solution starting from drug discovery to commercialization in India.

"There is a need for speeding the regulatory processes at all stages of drug development starting from seeking licenses for initiating drug discovery, conducting clinical trials in India to obtaining regulatory approval for commercialization. Other areas to look into include speeding up the patent approval process and addressing issues such as the definition of patentability and compulsory licensing."

Ang comments that the Indian government can look to the approaches adopted by other Asian governments. The Chinese government, for example, has abolished retail price caps and established a specialized court in November 2014 to handle intellectual property cases in Beijing. Japan's move to set up the Japan Agency for Medical Research and Development (AMED) in April 2015 also represents another initiative to boost drug discovery.

Future outlook

BMI remains optimistic with regard to India's pharmaceutical industry. "The development of new drug discovery in India has the potential to improve the overall healthcare system in the country. The introduction of new medicines will help alleviate the burden of diseases as it provides greater access to innovative medicines through the clinical trials conducted in India. The growth of the local pharmaceutical research and development sector can serve as a key driver of economic growth, and this will help increase income levels and improve the access to healthcare services," Ang says.

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Modernizing Scale-Up

Jennifer Markarian

Quality-by-design tools improve efficiency in scale-up of pharmaceutical processes.

Quality-by-design (QbD) methods, which focus on using science- and risk-based approaches to design a process, are increasingly being used in pharmaceutical process development and scale-up. A goal of QbD was to reduce regulatory burden and allow continual improvement within a design space. FDA is incorporating QbD concepts, for example, in its question-based review for new drug applications (NDAs) and abbreviated NDAs (ANDAs). Professionals at a growing number of pharmaceutical companies are finding that QbD-based strategies are more efficient and help achieve the goals of getting products to market faster with less expense, reduced risk, and more consistently high quality.

QbD reduces risk

In the small-molecule drug-substance market, a trend toward outsourcing

chemical development and early-stage manufacturing has created new requirements for streamlined technology transfer between companies and sites, note Steve Cropper, business development manager, and Joe Hannon, CEO, both at software provider Scale-Up Systems. “When you start to hand over reaction, workup, and isolation steps to be run at scale, often in different geographies, making a robust assessment of what is going to work becomes a priority,” explains Cropper. QbD tools allow an increased understanding of the process, which leads to a more robust and reliable process with reduced risk for scale up. “Application of QbD tools enables practitioners to ‘hit the sweet spot’ quickly,” adds Cropper. “So, even though chemistries may be getting more complex with more steps to scale-up, the right tools are enabling users to find the conditions where they can run

their processes to achieve their critical quality attributes (CQAs).” This holds true for both drug-substance and drug-product manufacturing.

“A change in scale-up strategy is identifying, characterizing, and focusing on scaling up the key drug product attributes rather than by scaling up process parameters using conventional scale-up principles,” notes Preetanshu Pandey, senior research investigator at Bristol Myers Squibb. “This strategy ensures more confidence on scale-up that, in turn, enables more development work to be conducted at small scale (i.e., minipiloting), leading to significant API savings,” says Pandey. “A part of the reason such a strategy is now possible is the introduction of new process analytical technology (PAT) tools that can provide that level of characterization, in addition to an enhanced understanding of relevant drug-product properties or key process factors that directly affect CQAs.”

“By enabling advanced process understanding, QbD reduces the risk of batch failure or the need for rework when changes are made,” says John Groskoph, senior director, global chemistry, manufacturing, and controls at Pfizer Global Supply. “When we understand our processes more thoroughly, we are better positioned to anticipate potential risks to product quality. The concept of connecting the attributes of the finished drug product back to the quality target product profile and, ultimately, to patient needs, is the foundation for any QbD program. Challenges do remain, however, particularly with how to use enhanced process understanding to enable post-approval changes in ways that may differ from established regulatory guidance.”

QbD approaches are increasingly used to provide a greater assurance of scale-up success with less need to troubleshoot or redesign after failure at a larger scale, says Christopher Potter, International Society for Pharmaceutical Engineering advisor and chemistry, manufacturing, and controls consultant. Using QbD approaches that incorporate a quality risk management (QRM) methodology reduces risk and facilitates scale-up. QRM involves risk iden-



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tification, analysis, and evaluation to produce parameters that can be investigated to enable risk reduction in the formulation and in the process design, Potter explained in a webcast on scale-up using QbD (1). A multi-functional team (i.e., scientists, manufacturing personnel, engineers, quality assurance personnel) is crucial for QRM, said Potter, because these experts can identify the risk factors, particularly those important to scale-up, during the development phase, rather than later. The team analyzes the process using tools such as fishbone diagrams to identify CQAs and potential critical process parameters (CPPs). QRM tools (e.g., failure mode and effect criticality analysis) can be used to produce matrices to show the relative risk of each CPP on relevant CQAs. Designed experiments are conducted on the high-risk factors to try to reduce risk, and the team reiterates the risk assessment if necessary. "As evidenced in public presentations, QRM

techniques are widely used by both innovator and generic companies," Potter told *Pharmaceutical Technology*. "There seems to be increasing use, encouraged by regulators, with, for example, the question-based review process operated in the US for generic product ANDAs."

Faster test results speed decisions

PAT using online, inline, or at-line methods produces real-time results, which reduces time in scale-up experiments because decision makers don't need to wait for off-line laboratory results before making adjustments. In addition, real-time data are more useful for troubleshooting and understanding what is happening in the process. "Rather than simply knowing that a batch failed, you know why it went wrong," explains Emil Ciurczak, principal at Doramaxx Consulting. "The constant flow of information also helps you continuously improve your process."

A PAT machine-vision imaging tool for inline particle characterization can

show processors, in real time, whether they are obtaining the properties they expected at scale-up. "Imaging can be used to 'fingerprint' a product for scale-up," explains Luke Kiernan, technical services director at Innopharma Labs. "You can take images of spheroids or granules at a 2-kg scale, for example, and look for the same particle size and morphology at a 100-kg scale."

Modeling

The speed and quantity of data collection from PAT, as well as high-throughput experiments and design of experiments (DOE) programs, while beneficial, can present a quandary. "A challenge for customers is to avoid drowning in a sea of experiments and data, especially when much of the data are not informative or important," says Cropper. Multivariate data analysis software can be used to help identify which variables are important, particularly when the impact of scale-up on a process is not as well under-

Choosing oral solid-dosage production processes: Could a classification system help?

A proposal for a drug-product manufacturing classification system (MCS) for oral solid-dosage forms, which would build on the idea of the biopharmaceutics classification system (BCS), was published in January 2015 (1). Written by specialists in the UK's Academy of Pharmaceutical Sciences (APS) MCS working group, the proposal has been discussed at various industry forums by primary authors Michael Leane, principal scientist at Bristol-Myers Squibb; Kendal Pitt, senior technical director at GlaxoSmithKline; and AstraZeneca's Gavin Reynolds. The system would gather existing knowledge and experience to categorize and describe the properties of an API that would enable manufacture of a finished drug product with a given processing route. The classification system would complement the BCS and help developers select a process for a given API and/or indicate how an API could be optimized for processing with a given route. "A common understanding of risk would help in choosing a solid-dosage manufacturing process and would provide targets for API particle engineering efforts," said Leane in an interview with *Pharmaceutical Technology*.

The processing technologies included in the classification system are, in order of increasing complexity: direct compression (DC), dry granulation (DG), wet granulation (WG), and other technologies (OT), such as melt granulation or liquid or semi-solid-filled capsules, for example. More complex processes can handle a wider range of API properties, but may have more steps or related costs. DC, for example, is the simplest process with only mixing and compression, but unfavorable API particle size and shape may be difficult for DC to handle. MCS would aid API development that seeks to engineer API particles to enable use of the simplest process possible for a given formulation. The MCS can also provide information for negotiations between CMOs

and pharmaceutical companies by providing a common understanding of API properties and what might be needed to produce a drug product.

The MCS would also facilitate scale-up to clinical or commercial manufacturing facilities. "The MCS would help ensure that the chosen process is more robust by putting the process in the center of the design space rather than at the edges," explains Leane.

"If you choose the optimal process, scale-up should be easier and have less risk," adds Pitt. "A more complex manufacturing process might have less worries about how the API will perform but more potential for troubles with scale-up. In granulation, for example, the wetting step could cause a form change; milling subjects the API to shear, and drying subjects it to heat. There are a lot more steps for something to go wrong."

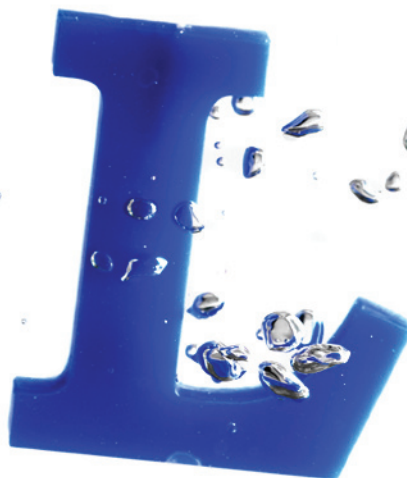
The MCS is seen as a simplified starting point that classifies only API properties. Interactions with excipients, for example, were not included in the outline. Although excipient choice can certainly affect a formulation, the working group felt that this might add too much complexity to the system. "Companies can use the MCS to perform their own proprietary, more detailed risk analysis that would include a company's own knowledge, preferences, and expertise based on their own therapeutic areas," suggests Leane.

The MCS working group plans to continue its discussions and present their ideas at the FIP World Congress of Pharmacy and Pharmaceutical Sciences (Dusseldorf, Germany, October 2015) to elicit suggestions and thoughts from industry professionals. The authors plan to subsequently publish another paper describing possible refinements to the system.

Reference

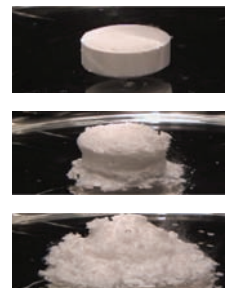
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stood or is complex, as is often the case in biopharmaceutical process modeling (see sidebar).

Using mechanistic, first-principles modeling, however, should be the first choice if possible, and software is available to help scientists and engineers apply fundamental principles without having to directly handle the math, says Cropper. In API manufacturing, for example, “Modeling software can quantify the effect of scale-dependent physical rates (e.g., mixing and heat transfer) on scale-independent chemistry (e.g., the rates of the main product and impurity-forming reaction steps) as well as crystallization and isolation. Linking these rates in a predictive model enables the scale-up and technical-transfer groups to visualize whether they will get the results they expect on scale-up and to select, or specify, the best equipment for their API steps. In short, it enables more confidence that scale-up will be successful in today’s accelerated development programs,” he concludes.

Modeling technologies enable process engineers to simulate changes in the process model and develop an optimized process and control strategy without running experiments on the actual process. This strategy saves time and cost.

Flowsheet models are process system engineering tools that can be used to improve control strategies and product quality for continuous manufacturing processes, note the authors of “Flowsheet Models Modernize Pharmaceutical Manufacturing Design and Risk Assessment,” in this issue of *Pharmaceutical Technology* (2). Because the equipment in a continuous manufacturing process is integrated in an end-to-end fashion, understanding the relationship each piece of equipment has on the product is not a trivial problem. Understanding the impact process variations have in the output of the system is crucial for quality control and risk management. Flowsheet models use the individual mathematical models for process equipment to create a model representation of the integrated continuous process in order to study the system *in silico*. Using flowsheets, the impact of process disturbances on the product properties can be simulated, which allows quantitative risk assessment and development of effective control strategies. Flowsheet models can be used for the design, control, scale-up, and assessment of continuous processes and can also help translate batch processes into an integrated continuous process.

Continuous processing

Continuous processing is being developed for API production, drug-product manufacturing, and, in some cases, for end-to-end production with no break between.

“Continuous manufacturing is the way of the future,” says Ciurczak. “Drug pricing pressure is pushing manufacturers to modernize to reduce costs, and industry has reached the tipping point for using continuous processes—NDAs using continuous processes have been approved and equipment is commercially available for anyone to purchase.”

Optimizing a continuous process with DOE uses much less material than DOE in a batch process and can be performed more quickly, because process conditions can be changed relatively quickly. Continuous processes are easier to scale than batch processes, and, in fact, can eliminate the need for scale-up at all because the process could, theoretically, be run for a short time to obtain a small-scale volume or a longer time to obtain a larger-scale volume, with both scales using the same equipment and processing conditions.

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Multivariate data analysis finds use in biopharmaceutical process development and scale-up

Multivariate data analysis (MVDA) is being used to effectively handle complex datasets generated by process analytical technology (PAT) in biopharmaceutical process development and manufacturing. From these large datasets, MVDA can be used to identify the parameters that are causing most of the variability in a process. These parameters can then be controlled to improve consistency in the process and product quality, noted Rathore and Singh in an article reviewing use of MVDA in bioprocessing (1). The authors gave an example of MVDA used in scale-up of a cell-culture process from 2 L to 2000 L. Data analysis showed that osmolality and ammonia levels were changed upon scale-up, indicating a change in cell-culture performance. The change in osmolality resulted from the buildup of carbon dioxide due to less-efficient gas transfer at the larger scale.

MVDA can also be used to establish comparability of processes and products, which is crucial for biosimilar development, noted Rathore and Singh (1). Chemometric algorithms can be used to compare different phases of manufacturing. Partial-least squares analysis of data in a laboratory-scale and a production-scale fermenter, for example, identified which variables were responsible for differences between the two scales.

Sartorius Stedim Biotech (SSB) recently integrated chemometric software into its microbioreactors used for bioprocess development. “Providing a consistent, scalable platform for design-of-experiment (DOE) studies and data analysis will help scientists develop robust and flexible manufacturing processes based on single-use bioreactor technology,” said Mario Becker, director of marketing, PAT and Automation at SSB, in a press release (2). He said that the MVDA toolkit would help reduce risk in bioprocess development and achieve more rapid, cost-effective production. The combination of microbioreactors and chemometric software can be used for media optimization, process parameter screening applications, and Monte Carlo simulations as part of a quality-by-design program to identify the desired operating region for manufacturing-scale processes, commented Barney Zoro, ambr15 product manager at SSB, in the press release.

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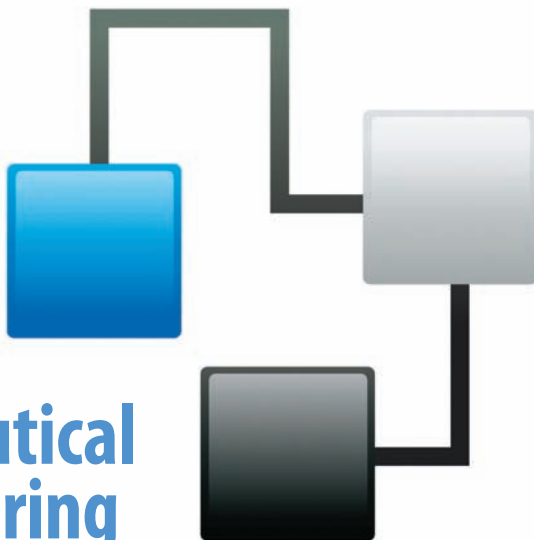


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Flowsheet Models Modernize Pharmaceutical Manufacturing Design and Risk Assessment



M. Sebastian Escotet-Espinoza, Ravendra Singh, Maitraye Sen, Thomas O'Connor, Sau Lee, Sharmista Chatterjee, Rohit Ramachandran, Marianthi Ierapetritou, and Fernando J. Muzzio

In silico design facilitates process optimization and evaluation of process control strategies.

The pharmaceutical industry has recognized the value of implementing a systematic approach to drug product development where quality is built into the product and process. The FDA initiative on quality by design (QbD) promotes the design of the product and manufacturing process using principles of chemistry, engineering, material science, and quality assurance to ensure acceptable and reproducible product quality and performance throughout a product's

lifecycle. Product quality is achieved through design of robust processes that are controlled and optimized using product and process knowledge (1, 2). In the QbD paradigm, mathematical models can potentially be used at every stage of drug product development and manufacturing (3). Modeling can help establish a predictive framework using experimental data and scientific principles to create mathematical representations of the system. Predictive models aid process design by evaluating

the impact that operations, equipment, and inputs have on product attributes *in silico*. Predictive models also provide a framework for risk assessment, process control, and optimization, where accurate predictions of the system are required (4).

In this article, the authors focus on the use of flowsheet modeling, a process system engineering tool for the design, development, and integration of pharmaceutical processes. More specifically, they discuss application of flowsheet models for process risk assessment and design of control strategies.

Process development paradigm and novel methods

Process design and risk assessment. Major components of the QbD approach to development include assessment of process risk and establishment of a design space. Risk is defined as “the combination of the probability of occurrence of harm and the severity of that harm” (5). Risk assessment is a science-based process used in quality risk management to identify and rank parameters (e.g., process, equipment, input materials) with potential to have an impact on product quality. Once the significant parameters are identified, they can be further studied to enhance process understanding, which could lead to the establishment of a design space (5). Design space is defined as “the multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality” (6). In general, a good understanding of potential risks when defining a design space can potentially reduce process uncertainty and increase process sustainability. Such knowledge can be used to establish a quantitative framework to measure how process failures impact product quality and determine a risk mitigation approach to reduce process-derived patient hazards.

Pharmaceutical process systems engineering. As the pharmaceutical industry modernizes its manufacturing practices

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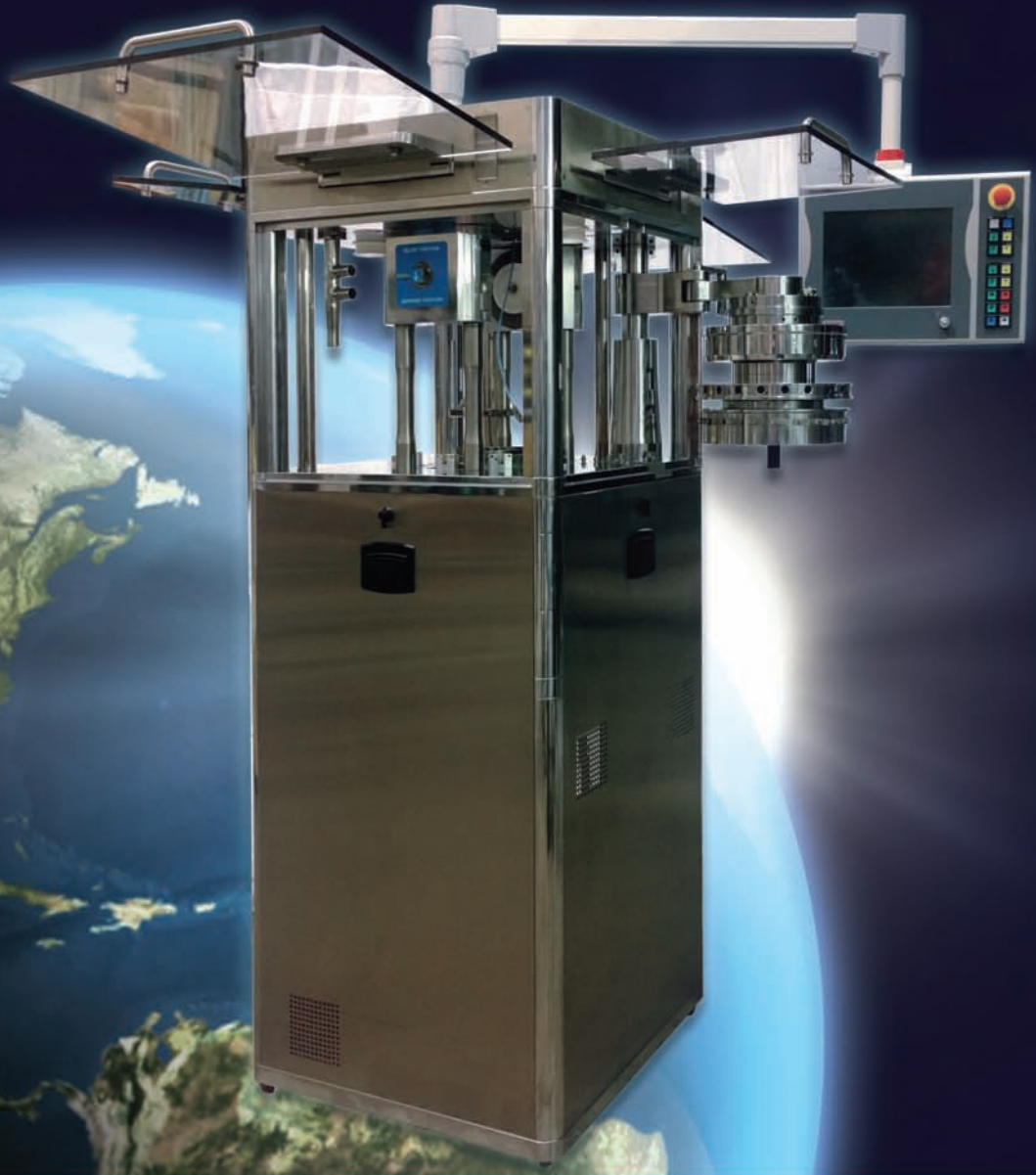
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PROCESS MODELING

and increasingly incorporates more efficient processing approaches such as continuous manufacturing, it is important to assess the process design elements that affect product quality for these emerging pharmaceutical manufacturing approaches. In designing continuous flow systems, while the analysis and optimization of individual process equipment remain important, the primary objective is to identify and evaluate design elements that pose a potential risk to product quality for the fully integrated system, leading to effective risk management. It is also important to consider the multivariate nature of such systems in process design (7). Within this context, process systems engineering (PSE) tools have been implemented with the goal of facilitating effective and efficient process design. PSE is the application of computer-aided systematic science and engineering approaches to the modeling, design, analysis, control, optimization, and operation of process systems.

PSE tools can provide insight to pharmaceutical development as a means of evaluating processes *in silico* (i.e., using a computer). Mathematical models embedded in the PSE tools can potentially supplement expensive and time-consuming *ex-silico* experimentation throughout process development (8). Furthermore, predictive mathematical models, once validated, can be used to study the process dynamics in detail, to help achieve high process efficiency, and to attain the desired product quality. These models can facilitate the design of processes where consistent product quality is achieved at every step of manufacturing within the framework of QbD and process analytical technology (PAT) (9). **Table I** summarizes the PSE tools (10) and their potential utility in pharmaceutical process development.

Definition of flowsheet models

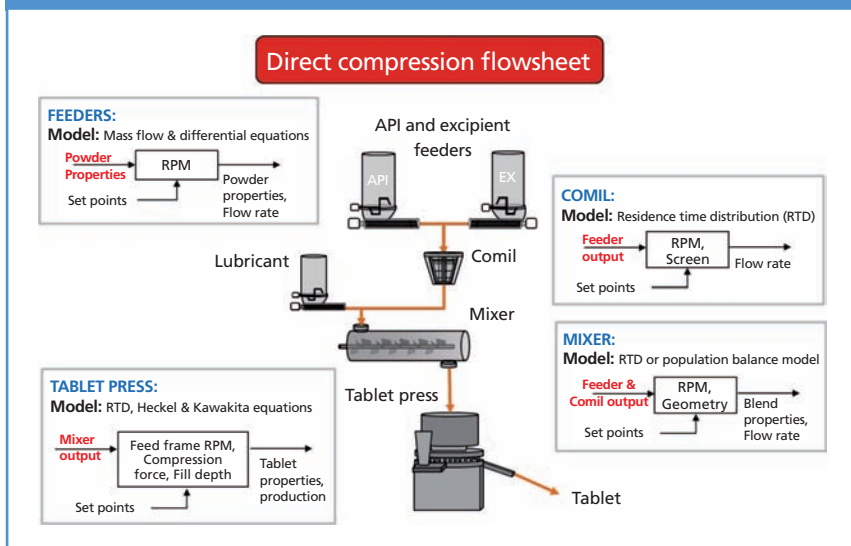
In an integrated process, individual pieces of equipment (i.e., unit operations) are connected in series. In such a process, a train of multiple units, one after the next, is connected with piping to perform powder-to-tablet manufac-

Table I: Process systems engineering tools for process development.

Process systems engineering (PSE) tools	Process development objectives
Predictive models	Process understanding
Flexibility & feasibility analysis*	Process parameter ranges
Flowsheet modeling	Process integration and simulation
Steady-state optimization*	Process and product design
Dynamic optimization*	Process improvement and efficiency
Sensitivity analysis*	Risk assessment
Controller design*	Consistent manufacture of desired critical quality attributes

*PSE tools used with individual and integrated (i.e., flowsheet) models. Adapted from "Integrated Simulation and Optimization of Continuous Pharmaceutical Manufacturing" (10).

Figure 1: Flowsheet models for a continuous direct compression system. The output from each unit operation model (represented as a schematic) is the input for the subsequent unit. These calculations are done automatically and sequentially in a flowsheet model environment (e.g., gPROMS, Process Systems Enterprise).



turing sequentially, without isolation of intermediates. The output of a preceding unit becomes the input of a subsequent one, with material continuously flowing between them. Mathematically, process integration follows the same logic. Individual equipment models are combined by taking the results from a preceding model and using it as the inputs of a subsequent one. The integrated process models are called flowsheet models, as the flow of information between the unit models resembles the flow of material(s) between unit operations. **Figure 1** shows an example of a flowsheet model for a

continuous direct compression system developed at the Engineering Research Center for Structured Organic Particulate Systems. Several flowsheet modeling software packages (e.g., ASPEN Plus, ChemCAD, gPROMS) have been effectively demonstrated for predictive modeling and design of fluid-based processes and are already widely used across the chemical and petrochemical industries (11). Flowsheet models have been recently developed for continuous pharmaceutical manufacturing schemes and have been shown to effectively capture integrated process dynamics (3, 12).

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Figure 2: Major drug-product manufacturing routes already modeled using flowsheet modeling approaches. While multiple routes are represented in this schematic, a single route would be modeled in each application.

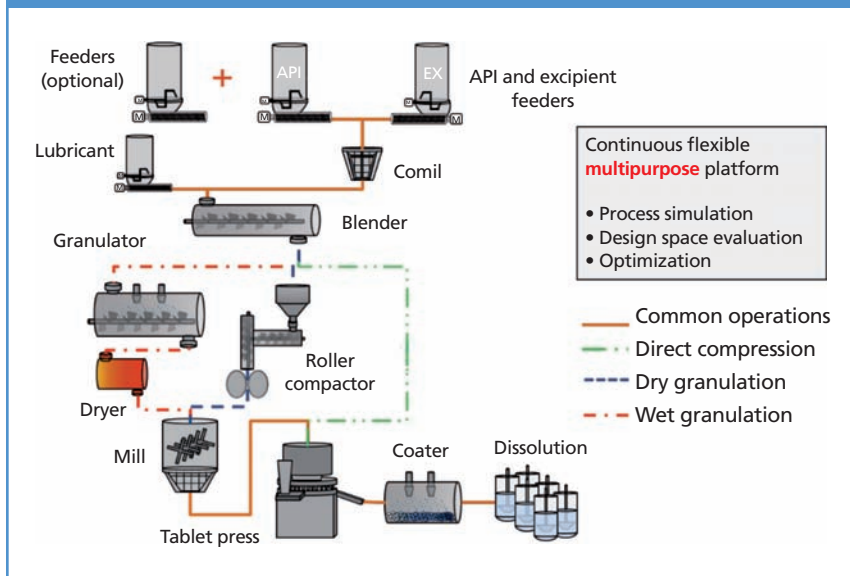
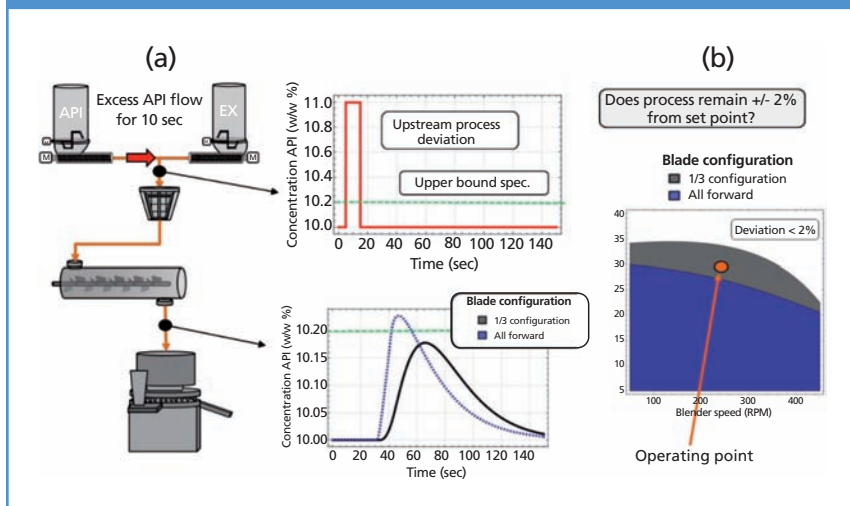


Figure 3: A risk assessment case study considers an upstream process deviation at the API feeder. Feeder and blender rates are 30 kg/hr and blender blade speed is 250 rpm. A flowsheet model system is used to evaluate the effect of the blender on mitigating a deviation in the feeder flow (a). The design space for the blending process at two different design blade configurations (all-forward and one-third-back configuration) is evaluated. The operational space for each blade configuration in this blending scenario is shown as the shaded regions (b).



Application of flowsheet models for process development

Flowsheet models, such as the one shown in **Figure 1**, can be used as a tool for process design, optimization (13, 14), risk assessment (15), control strategy analysis (16, 17), and moni-

toring of a continuous pharmaceutical process.

Process design and optimization. From a design standpoint, flowsheet models can potentially provide great value as a tool to evaluate equipment configurations and manufacturing schemes *in silico*

at a much lower cost than the equivalent experimental investigation. Using flowsheet models, the major routes for drug product manufacturing can be evaluated, and challenges with process scale-up can be anticipated and resolved (9, 12). Flowsheet models for continuous direct compression, dry granulation, and wet granulation, shown in **Figure 2**, have already been developed and demonstrated for their potential use in process design and optimization (15). Such multiplicity of models leads to a flexible flowsheet modeling platform that can streamline the design process compared to the relatively iterative and expensive, experimental and empirical-based process design approach.

Using flowsheet models, process engineers can study the system *in silico* and obtain information about process conditions that would lie outside the range of acceptable outcomes, and, thus, narrow the scope of subsequent experimental investigations. This information would naturally lead to more focused development efforts, which could eventually lead to a higher level of process understanding and establishment of the design space. The reduction in experimentation due to *in silico* evaluation reduces materials usage (e.g., API, excipients), waste, development time, cost, and personnel exposure, while it can potentially improve product quality. During process optimization, flowsheet modeling can potentially be used to determine optimal values for high-risk process parameters.

Risk assessment. Understanding the impact upstream operations have on the process is one of the critical aspects for assessing risk to product quality. Flowsheet models can aid risk assessment through the use of sensitivity analysis. This tool elucidates the impact different process variables and parameters have on the overall system performance and product quality. Case studies considering disturbances and their impact on the process performance using sensitivity analysis have been previously discussed (12, 15, 18). A simple example of risk assessment relates to whether a continu-



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Figure 4: In a control-variable selection and response-design case study, the effect of blender speed on the dilution of feed-rate disturbances is examined using a flowsheet model for a blender with the “all forward” blade configuration. The evaluation leads to the selection of appropriate control action (i.e., reduction of blade speed from 400 to 300 rpm or less) at the blender level, based on the upper bound set by the process.

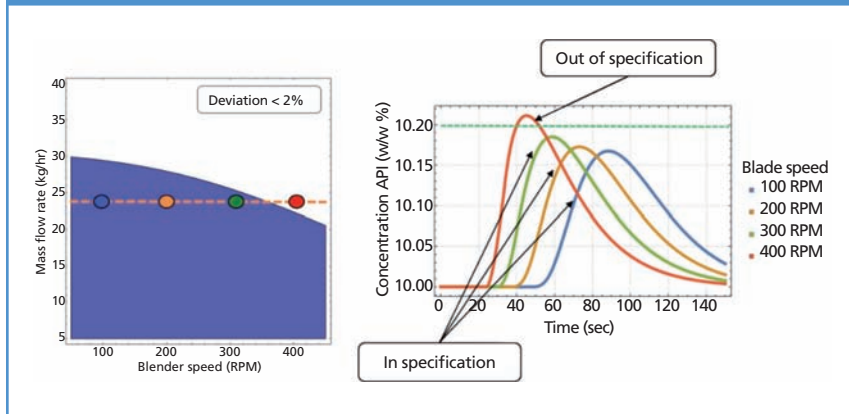
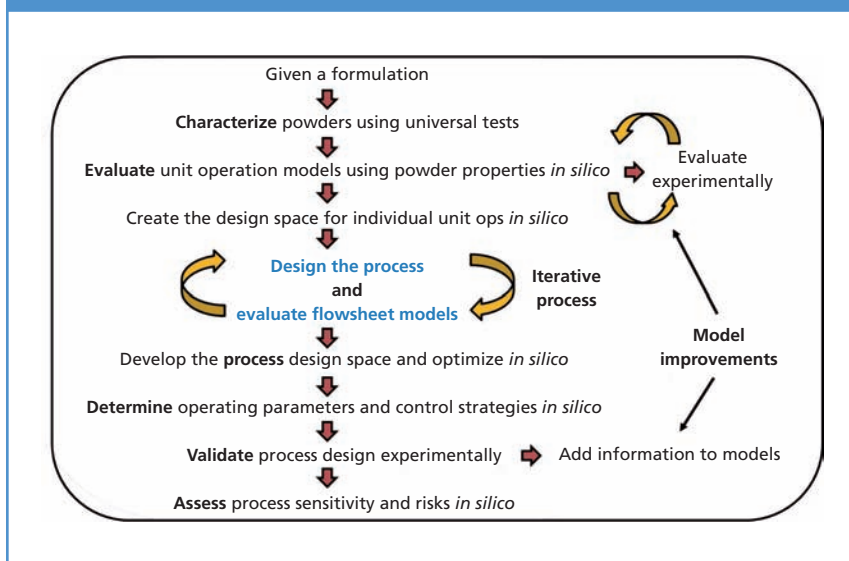


Figure 5: Process design and development algorithm using flowsheet models as the central method.



ous blender can sufficiently reduce the disturbances introduced by the feeders. In the example illustrated in **Figure 3**, flowsheet models are used to study the scenario addressing the question: “Will the blender keep the concentration within specified limits if one of the feeders overfeeds material for a short time?” The scenario was simulated by modeling the output blender concentration after the feed of API surges, leading to a change in concentration of the material entering the comil (i.e., the conical mill

between the feeder and blender) for 10 seconds. For comparison, two impeller configurations (“all blades forward” and “one-third blades back”) for the blender were simulated using pre-existing blender models to demonstrate the application of flowsheet models in the risk assessment.

The simulation illustrates the impact of the feeder and blender on the API concentration in the blend as a function of time (**Figure 3a**). Before the comil, the output of the feeder surged,

causing a 10% increase in the concentration of API, which was well above the (arbitrarily selected) permissible 2% upper specification represented with the green dotted line. After the blender, only one of the blade configurations (i.e., one-third configuration) was capable of mitigating the perturbation sufficiently to bring the output API concentration back within the specified limit. The operational space where the blender, given a blade configuration, would be able to dampen similar process disturbances is shown in **Figure 3b**. This type of analysis allows process engineers to understand the risk associated with each process parameter (e.g., blade configuration). Edges of failure, process sensitivity, and flexibility can also be studied using a similar approach (15).

Control system design and evaluation.

In the pharmaceutical industry, it is imperative to assure consistent manufacture of the desired product quality. To achieve this goal, material properties and process parameters need to be maintained within predetermined ranges. Deviations from the established ranges increase the risk of producing poor quality products. A process control system can be implemented to automatically adjust the process in response to disturbances to ensure that the quality attributes consistently conform to the established ranges. The design and implementation of an efficient control system is an interactive procedure that involves identification of critical controlled variables; coupling of the controlled variables with suitable actuators (manipulated variables); selection of monitoring tools; selection of a process-control approach followed by controller tuning; model-based, closed-loop performance assessment; and finally, implementation at the manufacturing plant through the available sensing and control platform integrated with control interfaces (19, 20). Integrated flowsheet models can facilitate the design, implementation, and tuning of process-control systems (21). *In silico* identification and evalua-

tion of process variability sources (e.g., blending) aid the selection and location of appropriate monitoring and control methods.

Using the same scenario modeled in the previous section, a case study was conducted to identify a suitable process control approach for mitigating a deviation in API feed rate. Using the flowsheet models, the process parameters for which adjustment can help mitigate the process deviation (i.e., potential risk) can be identified. The analysis conducted in this case study indicates that reducing the flow rate and, counter-intuitively, the impeller rotational speed can increase the mixing ability of the system. The increased mixing is able to mitigate the simulated disturbance, bringing the product back within specification as shown in **Figure 4**. This analysis therefore identifies blade speed and flow rate as potential control variables.

Flowsheet models can also provide knowledge regarding the process dynamics through estimation of the residence time distribution to determine the adequate in-process measurement frequency for process monitoring and control application. Furthermore, controller tuning and testing can be evaluated using flowsheet simulations prior to being implemented in the manufacturing plant.

Pharmaceutical process development using flowsheet models. Given the potential benefits of flowsheet models, a methodology for their use in design, optimization, control, and future process assessment is proposed in **Figure 5**.

The process begins with the characterization of materials, to assess whether the mathematical models for individual equipment are capable of predicting the behavior of the ingredients and intermediates (e.g., blends) in the process. If the material properties

are not within a unit's studied range, an experimental evaluation should then be performed to characterize the powder behavior in the unit, and the resulting information should be incorporated into the model.

Once individual models have been tested, *in silico* design spaces for these units can be created. Combination of the design spaces of individual unit operations using flowsheet models can then be used to propose a set of manufacturing process conditions that best suits the system. Subsequently, the process design space can be created and optimized. Target operating conditions and process control approaches can then be formulated. Once the process conditions and process control approaches are selected, it is recommended to experimentally verify model predictions. The experimental data collected can be used to further tune and improve model predictions as

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appropriate. After confirmation of the model's accuracy, risk assessment and process sensitivity are performed to ensure process robustness. The flowsheet models created during process design and development can then be applied to evaluate strategies for process monitoring and control.

***In silico* design through flowsheet models has had major impact in other industries, and it is reasonable to expect that it will also be transformative for pharmaceutical manufacturing.**

Potential regulatory application of flowsheet models

Risk-based regulatory approaches increase the efficiency and effectiveness of review and inspection activities by directing resources to focus more on the assessment of high-risk areas for products and processes. Quality risk assessments require product and process knowledge to evaluate potential sources of harm (e.g., failure modes of a process and sources of variability) and probability of detection of problems (5).

As discussed, continuous processing, compared with batch processing, offers a greater opportunity to develop and better use process models to gain process knowledge, because governing equations can generally be derived based on physical and chemical principles. Integrated process models can support a quantitative initial risk assessment through sensitivity analysis by examining the relative magnitude of the impact of variation in process parameters and/or material attributes on quality attributes.

As an example, in a published study, the most significant sources of variability for a particular continuous tablet-manufacturing process were found to be the mean particle size and bulk density of the raw materials (12). This type of analysis can then be used

to focus the regulatory assessment on whether a proposed control strategy is appropriate for mitigating the identified high-risk areas (e.g., variability in raw material particle size and density). Sensitivity analysis can also be used to guide the evaluation of advanced process control approaches employed by

identifying control and manipulated variables that should be incorporated into the control strategy (22). The process control strategy can be further assessed through the use of case studies, such as examining the processes' ability to mitigate the impact of disturbances (e.g., feeder refills). These case studies can aid regulatory review and inspection activities by identifying types of disturbances that may have a significant impact on product quality.

The level of detail required for describing a model in a regulatory submission depends on the impact its implementation has in assuring the final product quality. Integrated process models used to support process development and initial risk assessments by industry may be considered "low-impact models" because they are not used to assure the final product quality. Documentation for low-impact models should include a discussion of how the models were used to make decisions during process development. Integrated process models used for operating space determination or process control design may be classified as "medium-impact models." The International Conference on Harmonization Quality Implementation Working Group *Points to Consider* gives recommendations on documenting higher impact models (23).

The use of models by FDA to support review is not new (e.g., pharmacokinetic and drug adsorption modeling to support regulatory decisions with regards to bioequivalence and quantitative structure activity relationships models to risk-assess the potential toxicity of impurities). It is recognized that, although there have been significant advancements in the modeling and simulation of continuous pharmaceutical manufacturing processes, the technology is not yet sufficiently mature to aid regulatory assessment. To address this gap, FDA has sponsored two grants for the development of process simulation and model tools for the continuous manufacturing of solid oral dosage forms to facilitate the risk assessment of manufacturing process and control strategies. The goal is for these projects to lead to a collaborative platform for process simulation that builds on the process modeling knowledge developed in academia, industry, and regulatory bodies. The use of common risk assessment approaches and tools can facilitate the communication of risk mitigation approaches between industry and regulatory bodies.

Conclusion

In silico design through flowsheet models has had major impact in other industries, and it is reasonable to expect that it will also be transformative for pharmaceutical manufacturing. It could have major impact on the design process through the implementation of better, less wasteful, and smarter process design. It could also facilitate process optimization and process control, while minimizing development time. From a regulatory perspective, use of predictive models can enable a quantitative risk assessment, facilitating the quality assessment of manufacturing processes. It can also support the evaluation of control strategies by demonstrating system capabilities to handle multiple sources of variability, either individually or in combination.

contin. on page 86

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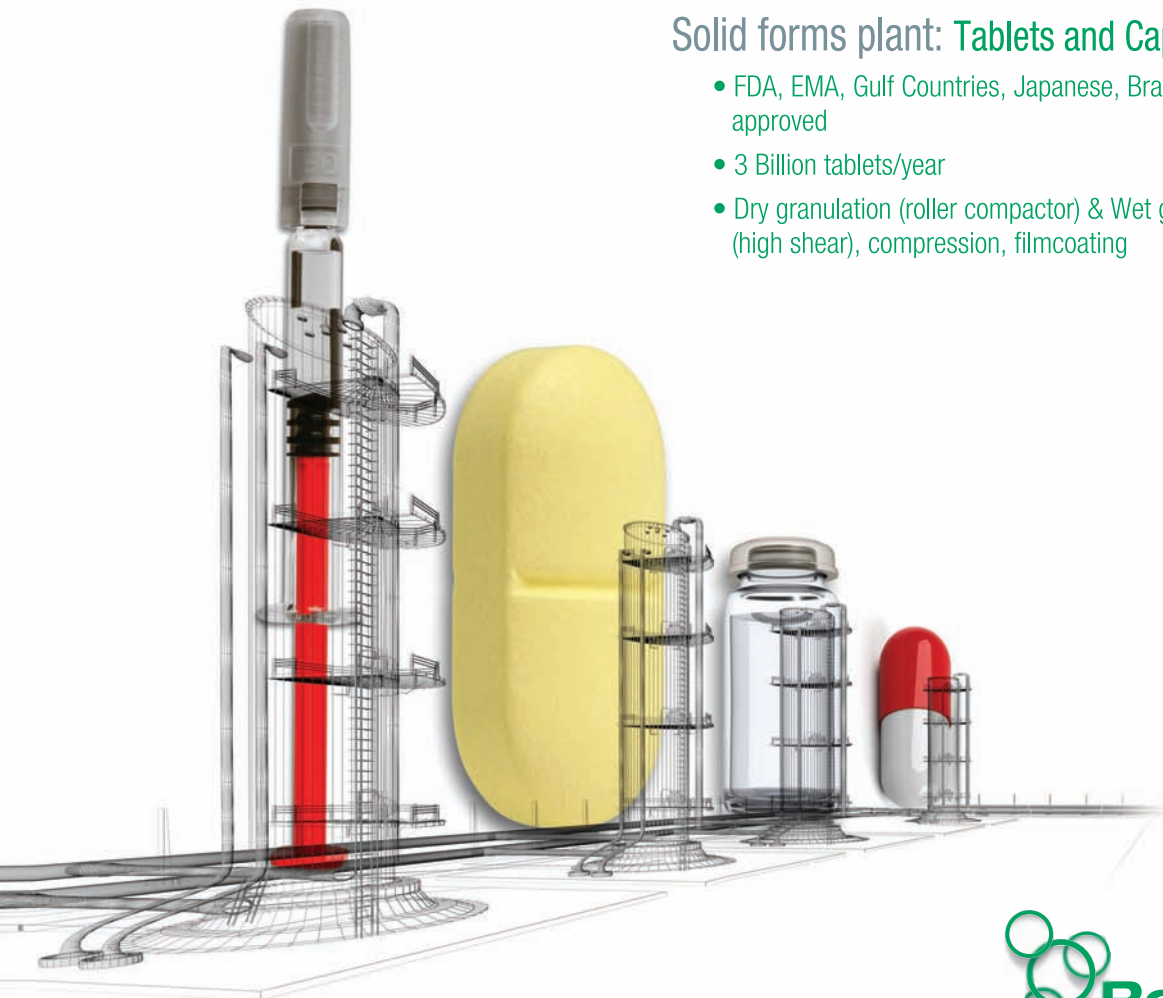
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FDA Steps Up Foreign Inspections

Cynthia A. Challenger

New legislation and changes in policy at FDA are leading to better control of the API supply chain.

In September 2011, the US Government Accounting Office (GAO) published a report on the challenges that FDA faced in assuring the safety of the API supply chain given that reliance on APIs produced by foreign manufacturers has risen dramatically and the complexity of the global pharmaceutical supply chain has increased significantly over the past two decades (1). The report found that while FDA had increased inspections of foreign API manufacturers (up 27% from 2007 to 2009, for example), its rate of inspection for foreign establishments was still far below that for domestic manufacturers. In addition, most foreign inspections were scheduled far in advance, conducted under controlled circumstances, and typically occurred during much shorter time frames. GAO also determined that FDA still lacked important information about foreign API manufacturers (1).

On a positive note, GAO recognized that FDA had begun to implement initiatives designed to improve its oversight of the drug supply chain, including increased training by overseas offices, the

development of programs for control of APIs and other drug products entering the United States, and a push for risk-based inspections rather than a set schedule (1). The GAO concluded, however, that FDA needed to implement changes more rapidly to better assure the safety of drugs on the US market (1).

Since that report, new legislation has affected FDA's ability to schedule and conduct inspections of API manufacturers. As a result, inspections of foreign manufacturers have increased dramatically—along with warning letters—while inspections of domestic manufacturers have decreased.

Impact of GDUFA

The most important piece of legislation affecting FDA's ability to improve the safety of the pharmaceutical supply chain is the Food and Drug Administration Safety and Innovation Act (FDASIA), signed into law on July 9, 2012. The Generic Drug User Fee Amendments (GDUFA), included as part of FDASIA, instituted a Generic Drug User Fee Program that was agreed to by FDA and the generic-drug industry, specifically the Bulk Pharmaceutical Task Force (BPTF) of the Society

of Chemical Manufacturers and Affiliates (SOCMA), the European Fine Chemicals Group (EFCG), and the Generic Pharmaceutical Association (GPhA).

The user fees are intended to provide additional funding for FDA's drug approval and inspection efforts with the goal of increasing the safety of generic drugs and the ingredients used to produce them, increase the speed of the drug approval process, and the transparency of the industry. One of the main goals of GDUFA is to ensure that foreign facilities are inspected at a rate equal to that of domestic facilities. The fees raised through GDUFA have enabled FDA to hire approximately 1000 additional employees, making it possible for the agency to complete more inspections and speed up the approval process for abbreviated new drug applications (ANDAs) and the review of drug master files (DMFs).

Further developments with FDASIA

Several other aspects of the FDASIA legislation have also impacted the API and formulated-drug supply chain. For instance, FDASIA requires FDA to identify facilities involved in the manufacture of generic drugs and associated APIs. "Prior to FDASIA, FDA didn't know how many facilities were producing formulated drugs or APIs in the US, let alone how many companies around the world were manufacturing APIs and formulated drugs and exporting them to the US," says John DiLoreto, executive director of BPTF. Before the self-registration process began, the industry estimated that there were 1700–2000 manufacturing sites around the world. After the registration process was complete, that number was reduced to approximately 1300. DiLoreto believes that some consolidation of manufacturing plants occurred as companies looked to reduce the GDUFA fees they would have to pay by consolidating operations.

In the most recent report on foreign and domestic drug establishments issued by FDA (2), the agency identified a total of 12,949 registered drug establishments in 2014, including 9330 domestic and 3619 foreign (slightly up from 12,613 in 2013). Of those 12,949 facilities, 4383 were registered as finished drug product (FDP) establishments, and 1495 were registered

Cynthia A. Challenger, PhD, is a contributing editor to *Pharmaceutical Technology*.

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as API establishments. (If a site produces both finished drug products and APIs, it is placed in the FDP category.) The remaining 7071 establishments fell into the “other” category, which includes facilities that produce, compound, or process medical gases, medicated feed, and some biologic drugs.

FDASIA also grants FDA the authority to confiscate and destroy unsafe APIs and drug products being imported into the US. With its increased ability to track the manufacturing activities and inspection histories of API and drug manufacturing sites, the agency can determine if APIs or finished drug products were produced at a facility that has not been FDA-inspected or is not in compliance. The agency has also published guidance on what conduct it considers as delaying, denying, limiting, or refusing inspection, actions that can result in determination of a drug to be adulterated. In addition, under GDUFA, all drugs produced in an unregistered facility or in a facility for which the GDUFA fees have not paid are considered “misbranded.”

“Together, these new capabilities of the agency make it possible for potentially unsafe APIs and drug products to be removed from the marketplace completely,” DiLoreto says.

FDA is also using the information on establishments to prioritize them according to the level of risk each represents. Rather than inspect facilities on a set schedule as was the case in the past—typically once every two and one-half years on average for domestic facilities and once every 10 years or more for foreign manufacturing sites—the agency now determines which facilities to inspect based on the overall level of risk they pose, which is determined using a model that takes into account inherent risk, outbreaks, recalls, adverse events, and compliance history (3). This move has led to a dramatic increase in foreign inspections and a concomitant decline in domestic inspections.

In fiscal year (FY) 2014, the total number of foreign and domestic high-risk human drug inspections by FDA was 918, which exceeded the agency’s target of 750 (3). In FY 2013, 443 domestic and 365 foreign high-risk establishments were inspected (total of 808); 43 GMP-based warning letters were issued as a result of those

inspections (4). Overall in FY 2013, FDA conducted 967 domestic and 604 foreign GMP inspections (3). In FY 2014, those numbers were 780 and 757. FDA estimates that in both FY 2015 and 2016, there will be 591 domestic and 843 foreign inspections.

Both the agency and the industry are adjusting to the risk-based inspection approach, according to DiLoreto. “When FDA first indicated that it would be decreasing domestic inspections so significantly, BPTF was initially concerned that domestic facilities would not be receiving inspections often enough, particularly those exporting to Europe, because the European Medicines Agency (EMA) requires pharmaceutical manufacturers importing products into the European Union to have had an inspection within the previous three years,” notes DiLoreto. The agency has addressed those concerns and established an agreement with EMA. “One of the primary goals of GDUFA was to achieve inspection parity between foreign and domestic facilities, but the change to a risk-based program allows FDA to better utilize resources,” he adds.

International agreements

An additional step in the right direction was made in December 2014 when FDA Commissioner Margaret Hamburg signed an agreement with Chinese officials to collaborate on inspections in China that builds on an initial agreement signed in 2007 (5). China also finally agreed to provide additional visas for more FDA inspectors, which will allow the agency to boost its number of employees from 13 to 33.

FDA is working with EMA on joint inspections and trying to establish mechanisms for sharing of inspection data, according to DiLoreto. BPTF would like to eventually see EMA and FDA inspections results considered to be equivalent. There are, however, concerns on the part of some manufacturers about how confidential business information can be adequately protected under such a scenario.

Ongoing issues

Despite the numerous advances that FDA has made in addressing concerns about APIs and formulated drugs manufactured overseas, there are still many challenges

facing the agency. Some foreign governments still do not welcome the agency, and inspections of foreign facilities still suffer from many restrictions. DiLoreto does believe, however, that the situation is improving in many countries, as indicated by the recent agreement in China.

There is also the issue of the dramatic increase in warning letters issued to foreign manufacturers that has occurred along with the rise in foreign inspections. DiLoreto expects these problems to be resolved once these manufacturers have been educated about GMP requirements and become familiar with the expectations of FDA. “It is not surprising that issues are being found at facilities that are being inspected for the first time. These facilities will implement the required improvements, and the number of citations will decline as more effective quality programs are put in place,” he observes.

It is also important to remember, according to DiLoreto, that many of the FDA inspectors now on the job are still quite new. “It takes at least two years for an FDA inspector to be fully trained, because it takes time for him/her to gain the practical experience needed for the job,” he says. “A large percentage of current FDA inspectors don’t have that two years of experience yet, and while new inspectors are on the learning curve, issues can arise,” DiLoreto continues. These difficulties, however, should also be resolved in the next few years, he notes.

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The Human Microbiome Project and Pharmaceutical Quality Control Microbiology

James Akers and James Agalloco



The Human Microbiome Project has increased our understanding of the relationship between humans and microorganisms. The authors offer a new perspective on how this knowledge should be considered in setting standards for pharmaceutical quality control in microbiology.

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One of the more exciting contemporary research activities in human biology has been the Human Microbiome Project (HMP) (1). The insights derived from the HMP have revealed details about the relationship between humans and the microorganisms we live with, and could not live without. In 2013, the first publications appeared that attempted to put the HMP reports into a pharmaceutical microbiology context (2). The purpose of this communication is to consider the HMP in the context of other recent insights into microbiological control and to explore how this knowledge could (or should) change the way standards are set for healthcare products. Microbiological analysis will also be explored with due consideration of what has been learned since the standards have evolved.

Fundamentally, the HMP provides far more expansive and accurate data regarding a topic that has long been of great interest, which is the nature, size (i.e., population), and scope of what's been typically referred to as normal human flora (3). Normal human flora is a generic and loosely defined phrase used to describe the myriad organisms with which all healthy (and not so healthy) humans are colonized. In many industrial microbiological investigations, one may read that an organism recovered is a constituent of normal human flora (4). When an organism is categorized as a constituent of the normal human flora, that is generally understood as an indication that it is relatively harmless. So, normal human flora can often take on a distinct meaning for current good manufacturing practice (cGMP).

However, data in the published HMP reports have confirmed something many academic microbiologists have long suspected, that many humans also have in their normal flora known "opportunistic pathogens" as well. These are organisms that inhabit a quality control microbiology gray area in that, as their name implies, they are able in very rare circumstances to cause human disease. Before considering the gray area and its implication in detail, an examination of some additional history of the HMP is required.

The HMP was initiated by the United States National Institute of Health in 2007 and grew into a research consortium comprising some 80 global research sites (5). The initial study findings were released in June of 2012 in a set of articles published in *Nature* (2–4). These studies

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were conducted on 242 healthy volunteers (129 male and 113 female). A total of 15 sample sites were selected for the male subjects and 18 for females. Continuing research is underway on study cohorts with different health conditions, including children with frequent fevers, individuals with upper respiratory tract infections, and pregnant women. Additional HMP work will, therefore, be published in a steady stream during the next few years and probably beyond.

The coining of the term microbiome is generally attributed to Nobel Prize-winning microbiologist/molecular geneticist Joshua Lederberg. Lederberg hypothesized that microorganisms living in the various environmental niches available on humans and animals played a more significant role in health and disease than had been generally recognized. The human microbiome can be defined as “the ecological community of commensal, symbiotic, and pathogenic organisms that share our (the human) body space” (6).

It is useful to examine the contents of this definition a bit further, because it contains words and concepts that may not be familiar. The definition first mentions a community of microorganisms living within the human “ecology.” This implies interaction among the organisms that may be present. In other words, the microbiome idea as Lederberg saw it was one in which organisms cooperated and interacted with both each other and human cells. Next, the definition mentions organisms that could be commensal, symbiotic, or pathogenic. A commensal relationship is where one organism benefits from suitable living conditions on another living species without adversely affecting that organism. A symbiotic relationship is one in which both organisms, for example a human and a bacterial species, benefit from the interaction. A pathogenic relationship is one where the circumstance by which an organism lives on another causes a disease in the other organism. The term pathogen is most critically and significantly applied to a microorganism known to have caused a human infection. A true or frank pathogen is an organism which, when recovered from man, is almost always associated with an infection. True pathogens may be viruses, bacteria, parasites, or fungal species.

Pharmaceutical quality control microbiology, the goal of which is product safety, is quite properly fixated on the prevention of infection. Naturally, this leads to the focus on the role of microorganisms as pathogens. The principal reason for concern about microorganisms as contaminants is that failure to limit their transfer from a medication to patients could result in human disease. The fear of microorganisms causing disease as a result of using a medication takes us from the realm of industrial microbiology into another specialty of the multi-faceted discipline of microbiology, namely the study of infectious disease. The study of infectious disease is a different activity from industrial microbiology, although the two overlap when the discussion turns to infection risk.

The study of infectious disease is not new. The formal study of the infectious disease began with reports of research done by Robert Koch, a German physician of the

late 19th and early 20th century. Koch, who won a Nobel Prize for medicine was effectively the founder of medical microbiology. Koch formulated a set of simple, but rigorous postulates that medical microbiologists and physicians use to positively attribute disease causation to a single species of microorganism. Four criteria that were established by Koch to identify the causative agent of a particular disease are as follows (7):

- The microorganism (pathogen) must be present in all cases of the disease
- The pathogen can be isolated from the diseased host and grown in pure culture
- The pathogen from the pure culture must cause the disease when inoculated into a healthy, susceptible laboratory animal
- The pathogen must be re-isolated from the new host and shown to be the same as the originally inoculated pathogen.

Scientists have had more than a century to investigate the causes of human infectious disease, and enormous progress has been made in developing both preventive medicines such as immunizations and treatments such as antibiotics for various infectious diseases. It is also possible to prevent or control deadly disease without knowledge of the causative organism. Two notable examples of this are smallpox and yellow fever. Edward Jenner created a vaccination for smallpox without knowing that the agent was a microorganism, or more specifically, a virus. He was able to do this in 1798, well over 100 years before the word virus entered the scientific lexicon and prior to Paul Ehrlich’s work, which led to the first understanding of a field that came to be known as immunology (8). The smallpox virus will not be found as a constituent of the HMP. In fact, no true (“frank”) pathogens were found in/on healthy humans, and conventionally, are found only in/on people suffering from a disease caused by that particular pathogen.

Consider for a moment that the HMP has found that humans have associated with them upwards of 10,000 different species of bacteria. The exact number of different species of bacteria on earth is unknown, but estimates range from hundreds of thousands to a billion. The pharmaceutical world often discusses “bugs” as microorganisms; bacteria and mold are viewed in the industry as though any recovery of these bugs above some numerical trigger point portends grave risk to the product’s end user. The vast majority of environmental isolates or “bugs,” enumerated from product or excipient tests, are completely harmless commensals or organisms from the environment external to the manufacturing plant. The overwhelming majority of organisms on our planet, including those that live in or on humans, are completely harmless. It may then be surprising to learn that the World Health Organization reports that more than 90% of all human infectious disease is caused by only six infective sources. Of these six diseases, four are caused by a single microorganism (9). The six types of infections that kill the most individuals worldwide in descending order of prevalence are:

- Acute viral respiratory infections including influenza (which is actually a disease cluster caused by a number of different types of viruses)



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The industrial microbiologist will notice immediately that the “bugs” responsible for these six primary infectious diseases are extremely unlikely to be found in healthcare products. Additionally, none of the viruses, or the malarial parasite, could ever be recovered by the prevalent microbiological analysis methods in use. Some of the viruses listed above are actually used to make healthcare products—live attenuated measles and influenza vaccines to cite to notable examples. Safety in the manufacture of those products obviously hinges on the ability to achieve effective attenuation. However, the majority of healthcare products, including all small-molecule pharmaceuticals and devices, could not harbor these organisms and therefore need not be tested for them.

Although studies on the viral component of the microbiome are underway, the viruses responsible for acute diseases are also unlikely to be found among the organisms recovered from normal healthy subjects. Some of the viruses that cause human illness are likely to be found, including herpes simplex I and varicella zoster. Per cGMP rules worldwide, people that are actively ill and manifest symptoms of infectious disease, such as fever, coughing, and skin lesions, should not be working in healthcare product production environments. However, it would be impossible to remove staff who carry herpes simplex 1 or varicella zoster. Attempting to do so would diminish the pool of qualified workers by more than 99%, because nearly every healthy human carries these viruses. Fortunately, it is possible in the modern world to immunize healthy humans against many of the common viral or bacterial diseases that continue to cause massive human misery.

The HMP data confirm that true or frank pathogens are not commonly present in normal human microflora. These data should reinforce the reality that real risk comes not from organisms that are part of our natural flora residing in the various environmental niches our bodies provide, but rather those that are associated with humans in significant numbers only when they are ill.

An obvious conclusion is that given their comparative rarity, those few species of microorganisms responsible for nearly all human infectious disease must have special characteristics; or those who are affected by these organisms must be particularly susceptible to them. Actually, both the condition of virulence (the ability to cause disease) and susceptibility (on the part of the individual) must be present for the result to be a serious clinical infection. Most human infections are either minor or completely

asymptomatic, which is to say we don't know we have them.

Some readers will be familiar with the staggering bacterial numbers reported by the various HMP studies that have appeared. With the identification of more than 10,000 bacterial species in the human microbiome so far, it is unsurprising that most of the known bacterial genera have been observed in association with healthy humans. The sheer number of total bacteria found in or on humans is an amazing $\sim 10^{14}$, which is approximately 10-fold more than the number of human cells each of us contain. Obviously, the 1–2 kg of bacteria that constitute our normal flora are responsible for neither harm nor undue health risk within their particular niches or none of us would make it to adulthood. This should inform the reader that the sheer number of microorganisms in a product is unlikely to meaningfully change the population of bacteria present at the site of administration.

It is long known that certain bacteria help protect us from disease, and assist us in digesting food, as well as other positive contributions they provide. A new peer-reviewed scientific journal has appeared entitled *Beneficial Microbes* (10). This should not surprise anyone because humans routinely consume milk products supplemented with bacteria, yoghurt containing active cultures, or probiotics containing millions of live bacteria. The concept of beneficial microorganisms is clearly at odds with “the only good bug is a dead bug” mentality that so often prevails in the pharmaceutical industry. This concept also confirms that the consumption of hundreds of thousands or even millions of colony forming units (CFU) of bacteria in food or within a probiotic capsule can be safe given that humans have done this for thousands of years.

The HMP has irrefutably confirmed how ubiquitous microorganisms are on and in humans. More importantly, it must be acknowledged that the overwhelming majority of microorganisms living in and on humans and present in the environment are either helpful or harmless. We need not worry about microbial risk arising from vast number of organisms associated with a healthy human. Nor should they cause any additional concern when they are released into work environments as they inevitably must be. The HMP should not give any thoughtful microbiologist or standard setter cause to embark on a campaign for tighter standards, more monitoring, or more intensive product testing. Nor should it cause an increased drive to expand the lists of so-called “objectionable” organisms. Obviously, there are no more microorganisms associated with workers now than before 2012 when the first HMP data appeared. There are no more microorganisms associated with people in 2014 than there were in 1714 or 1914. The HMP hasn't uncovered any increased or previously unknown risk potential—the only thing that has changed is an expanded knowledge of human biology. It may, in fact, lead to an understanding that the risk is not as great as some recent initiatives on microbial control for pharmaceutical products would indicate.

Instead of an increased and completely unnecessary fear of previously unknown microbial risk factors that might be present, the HMP results should cause us to marvel at the wondrous complexity of cross species interaction and to appreciate how much more interesting human biology is than previously imagined. We should instead feel comforted by the fact that the only organisms conspicuously absent in healthy human subjects during the HMP studies were frank pathogens. Although that is not new information, it is important to recognize that the average healthy human is colonized at all times by organisms that under certain circumstances may cause disease in some people. For example, approximately 30% of the healthy subjects in the HMP had *Staphylococcus aureus* present in their anterior nares. This does not mean that *S. aureus* should be tolerated in medicines. It does, however, teach us that even those who don't carry this organism are exposed to it on a daily basis, which should help keep the risk in perspective and consider it on the basis of product type and route of administration.

S. aureus is present on the skin in some humans and behaves as a commensal organism unless it reaches an environmental niche where it can grow unchecked. This means that if it is present, but goes undetected, dangerous conditions are unlikely, because in their daily lives, humans must encounter this organism on a frequent basis. It also means that because three out of 10 humans have this "bug" in

their noses, it must routinely be released into the workspace. Certainly the ubiquity of *S. aureus* in man confirms that the use of reasonable infection control procedures, such as routine hand washing and the use of protective masks in production areas, are reasonable precautions.

Perhaps ironically, the greatest risk from pathogenic strains of *S. aureus* has arisen from efforts to treat infections. This risk did not arise as a result of *S. aureus* in product, but rather from a misuse and over-use of antibiotics. Humans have forced the evolution of dangerous and hard to treat strains such as methicillin-resistant *S. aureus* (MRSA) by prescribing antibiotics to patients suffering from common viral upper respiratory diseases against which antibacterial agents have no value (11). The emergence of MRSA and other manifestations of antibiotic resistance is an example of the law of unintended consequences at work in medical microbiological risk abatement gone wrong. As it turns out, the misuse of prescription drugs has created much of the modern day risk regarding healthcare system acquired infections. Contrastingly, the actual microbial contamination of drug products has proven to be an insignificant contribution to human morbidity or mortality.

The HMP's findings regarding the content and staggering diversity of the human microflora increased the knowledge, but did not identify any new microbial infection risks. Personnel donning gowns to enter clean rooms or working

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in non-sterile product manufacturing don't have more microorganisms on or in them than they did previously. In fact, it was already known that the numbers of bacteria carried by humans were enormous and that they sloughed large numbers of recoverable viable bacteria into the environment even when aseptically gowned (12). The contamination control challenge hasn't changed, patient risk hasn't changed, and a push for more regulation accompanied by new (and presumably more restrictive) microbial control requirements should not begin as a result of the HMP. What has changed is the understanding of human biology and this should manifest itself as a keener appreciation of the absolute futility of "the only good bug is a dead bug" mentality. The HMP should not be a cause of new cGMP requirements through the regulatory inspection process or as a result of compliance fervor.

What the HMP and other recent studies are confirming is that humans all have on, around, and in them, far more microorganisms than ever thought possible a decade ago. More importantly, it also demonstrates that despite the incredibly high numbers of species and overall population, nearly all of these organisms do no harm and may even play significant roles in keeping us safe from other bacteria that are not part of the natural ecology. Perhaps the fixation with the numbers of organisms in environments inhabited or presented to humans needs to be reconsidered. Worries about absolute numbers of human commensals and symbionts in the environment are not rational where they do not correlate with an increased concentration of true pathogens in products or a threat to the patient's health.

Bacterial enumeration and patient safety

The healthcare industry has developed a number of standards that purport to set microbial "limits" for non-sterile products. The industry has also evolved target values for various production environments. The HMP findings suggest a reevaluation of how these limits were set in the first place. The more complete picture given by the HMP was made possible by the application of microbial analytical technology based on molecular biology. Previous attempts to evaluate and quantify "normal human flora" depended on the growth of bacteria on media and the enumeration of these organisms on solid media plates as introduced in Koch's laboratories more than a century ago. In other words, all previous studies on human microflora came down to counting colonies (CFU). The reliance on the CFU as the standard of cell-count estimations must change as we move to the modern analytical tools that made the HMP possible. The modern methods used in the HMP are called somewhat imprecisely "rapid" microbiological methods (RMM).

Some readers may be puzzled as to why the switch to molecular biological methods would result in different numbers than those that were obtained using growth-based methods and reported in CFU. There is a prevalent belief structure in the compliance world that growth-based methods have good, even a nearly perfect, limit of detection.

The existence of an analysis, boldly named the sterility test, implies that growth-based methods can and should be able to detect down to one cell. Recently, in personal communications, the authors have heard both regulators and industry representatives state that any new sterility test should have a limit of detection of one CFU. This is a clear example of a widely held compliance belief failing to come anywhere close to the scientific reality.

The problem with growth-based methods is quite simple; they can only "recover" organisms that will grow on the media selected under the incubation conditions offered. There are many presentations given in the industry in which there is an underlying expectation that Trypticase Soya Broth or Agar (TSB or TSA) will grow essentially all microorganisms if the right incubation temperatures and duration were selected. This statement has actually been known to be untrue for decades.

The "great plate count anomaly" was first reported in environmental bacteriology, but is now known to be generally applicable (13). Microbiologists noticed that when they viewed a sample preparation under a microscope and counted the bacteria present using a cytometer, there were often 100–1000 fold more cells present than grew on the agar plates. This observation led to a great deal of research regarding the formulation of media that would better recover a larger number of the cells present. Some of these efforts bore fruit and better recoveries were noted; a simple and limited example is the use of R2A agar rather than plate count agar for water analysis.

Changing to a different media formulation, however, will not eliminate the plate count paradox, it will only change the type of organisms recovered. One might recover organisms with a media change missed by TSA, but at the same time no longer recover some species that grew on TSA. One might increase recovery by 10-fold and still only recover a low percentage of the cells actually present. A laboratory could employ 10–15 different media each with different nutritional profiles and incubate them at different oxygen tensions or temperature ranges and still only manage to recover a limited amount of what actually may be present in a sample. This of course would be highly work intensive, and prohibitively costly in process, validation, or final product analysis. Such an effort could be logically deemed impractical given the limited expected improvement in results.

The different environmental niches on and in the human species cater to organisms with widely different nutritional requirements, and these niches also include certain symbiotic relationships between organisms that prove difficult to reproduce in a laboratory. The identification of molecular survival factors for organisms living in a given niche is an area of active research. Molecular genetics and biochemical analysis together can provide the means to better describe what niches exist within the human organism that favor the colonization by some species, but not others, in ways that would be impossible were they to rely on growth methods. Niche suitability can depend on

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availability of suitable nutrition, presence or absence of oxygen, perhaps pH, or the presence of other organisms that may produce needed nutrients or modify the niche to make it suitable for a symbiotic species.

Microbiology is a far more complex science than is allowed by the generalizations made in pharmaceutical microbiological standard setting and quality control analysis. Such a wondrously complex field of work does not easily yield to convenient assumptions.

Implications of the HMP on the patient

The implications of the HMP on the patient can be summarized as follows:

- An overwhelming majority of all serious human infections are caused by organisms not found among the human microbiome.
- Opportunistic pathogens are not consistent, predictable sources of risk. Because nearly all humans carry these organisms, it clearly means they are harmless within their normal environmental niches, and risk arises only when host susceptibility allows infection
- The HMP results do not suggest a need for increasing environmental monitoring (EM) intensity for any type of pharmaceutical product. The EM results only show what grew on the media selected and skew toward organisms that grow on the media used. The idea that EM results provide meaningful value in terms of assessing “sterility assurance” is absurd. They provide only a limited, but often useful, assessment of general conditions within a work space.
- The strict focus on enumeration of microorganisms in products is misplaced; the target values established in CFU weren’t chosen based on infectious disease data, but rather were selected in a largely arbitrary fashion.

Implications of the HMP for microbial control of oral and topical dosage forms

If the typical oral dosage of a tablet or capsule would be accompanied by perhaps 120 mL of water (four fluid ounces) using the current water quality limits for drinking water (in CFU), this would equate to no more than 300 CFU/mL or 36,000 CFU. Assuming that most water falls well below the limit and is generally not more than 150 CFU/mL, this means that along with a tablet or two, the patient would receive ~18,000 CFU of bacteria in the water they used to take the medicine. With that in mind, limits in the range of 10^3 CFU for oral solid dosage products are extremely conservative.

Recent studies on potable water using molecular biological methods for microbial cell enumeration, however, indicate that 120 mL of drinking water is more likely to contain 100–1000 times more cells than those recovered using traditional plate counts as reported in CFU. Logically, then, testing non-sterile pharmaceutical products with more modern microbiological methods results would likely result in higher observed cell counts; however, there would be no added patient risk in a product historically known to be safe.

Similarly, any suggestion that we need to be more concerned with sloughing of bacteria from personnel more now than before the HMP is clearly wrong, if anything, the obverse is true as the patient has a comparable number of microorganisms present on/in them as well. Newer molecular biological technology has improved the ability to identify and roughly enumerate a far broader range of cells.

The sheer numbers of bacteria counted on man or in the water we drink should not be sources of increased concern among regulators or microbiologists. They should not result in calls for new standards or new compliance requirements. They do not suggest wholesale changes in what we do, but they do suggest that we should be less fixated on the total numbers of bacteria around or on us. Therefore, we should not fear that which we have been ignorant because nothing has changed with respect to our exposure. As we learn more about microbes and their relationship with man, we must recalibrate our own thinking and allow scientists, including healthcare professionals, suitable discretion to make reasonable risk judgments. The following points should be considered:

- In the case of orally administered products, the natural flora already present are up to 10^9 cells according to the HMP, and the utter folly of fixating on some magic number below which safety begins should be absolutely clear. As oral products are commonly taken with water, obsession over the microbial population is un-warranted.
- Microbial limits given in the compendia are extremely conservative and products complying with them are safe for human use when assayed using current growth-based assays. There is no reason to hold to these precise CFU cell-count estimates when molecular biological methods are employed to assess these products.
- Any proposal for more intensive microbial assessment or added control requirements is unnecessary and would only increase costs without benefit to the patient or customer.
- The approach defined in *United States Pharmacopeia (USP) <1115> (14)* is sound as it places appropriate emphasis on actual sources of microbial risk, such as water systems, equipment design, equipment cleaning, and raw material control, while placing considerably less emphasis on environmental monitoring. The focus should be on materials that the product directly contacts.
- Absolute prohibitions against any microorganism (whether “objectionable” or not) in non-sterile materials are inappropriate for at least two reasons. First, there’s a good possibility that the patient already has that microorganism in/on them as part of their personal microbiome (the presence of microorganisms is not limited to manufacturing personnel). Second, there are no readily available means to selectively exclude any particular microorganism without the introduction of a sterilization step in the manufacturing process.
- Intensive testing of products that are inherently antimicrobial or have very low water activity is a non-value added

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Implications of the HMP for microbial control of sterile products

The implications of the HMP for microbial control of sterile products can be summarized as follows:

- The implications of the HMP on the patient can be summarized as follows: Perfection, or absolutely sterility, in microbial control when humans are present simply isn't possible. The number of microorganisms present on operating personnel means that even after properly donning sterile gowns, those personnel will continue to disperse microorganisms into the aseptic environment. Initiation of extensive investigations when an operator glove or gown is found to be >1 CFU is a fool's errand.
- Isolators and restricted access barrier systems (RABS) offer advantages because there are no personnel present, but their use need not be mandated as there are no serious risks associated with appropriately designed aseptic processing performed under manned conditions. The past 30 years of sterile product history suggests that the risks of infection associated with aseptically filled sterile products is substantially less than the infection risk associated with an overnight stay in a hospital.
- Requirements for sterility testing of validated terminally sterilized products are obsolete. Parametric release should be the default practice for all terminally sterilized materials.
- Regulatory expectations for "0" CFU count results from all environmental monitoring samples are unrealistic. It is inappropriate to consider non-zero counts as evidence of microbial contamination in the products. Given the population to be contained and the inadequacies of all current gowning systems, low counts should be both expected and accepted. Where advanced molecular or spectrophotometric methods are used to assess the environment, higher estimated cell counts are likely to be observed. This does not require a regulatory compliance reaction, because as has been long known, growth-based methods underestimate the number of cells present.
- The risk of significant microbial contamination in sterile products manufactured by industrial producers is extremely low. Regulatory compliance concerns for aseptic processing deficiencies are not based upon evidence of contamination in the products, but upon unreasonable and perhaps unnecessary expectations for "sterility" in environmental monitoring.

Further considerations on product safety and human biology

There is a valuable lesson to be learned from the events associated with the contamination of aseptically manufactured steroidal injections made by an unapproved pharmaceutical manufacturer that has so far resulted in more than 50 deaths

and approximately 730 injuries. In this outbreak, steroidal injections were contaminated with an environmental mold that would under normal circumstances be non-pathogenic. This outbreak, however, was in some respect, a perfect storm, because the injections of these products were made into the spinal cord and cerebrospinal fluid that have no normal flora. In addition, the immune response within the central nervous system is limited in its capacity to deal with microorganisms that would not normally be found there.

Humans come in contact each day with millions of mold spores of the type that caused the infections within the spinal cord. Humans are evolutionarily well adapted to dealing with such spores on their skin or drawn into their upper respiratory tracts. However, the manner of use of these contaminating steroidal injections and the particular characteristics of the injection target resulted in substantial risk. The combination of patient type and injection location with product made under substandard conditions in a facility colonized by mold resulted in a tragedy of substantial proportion. Further contributing to this disaster is the fact that treating a mold infection of this kind in the spinal cord is extremely challenging.

Thus, we are reminded again that introducing organisms into an area of the body with no natural flora and with limited immune response has substantial inherent risk. A product that should have been made with great attention to quality standards given the inherent dangers was instead produced under woefully inadequate contamination control conditions. The result was a human tragedy of a magnitude rarely associated with the use of commercially manufactured medicines.

Conclusion

The HMP research that has been reported should not serve as an excuse for new regulation, new performance standards, and certainly not new compliance initiatives. If we accept what the HMP is informing us about the reality of human/microbial interaction, we may instead see a redirection of our microbial control efforts to those areas where patient safety can be improved, rather than on those where the potential for harm is slight, if present at all.

It is also a time to reflect on human biology and to appreciate how humans and thousands of microbial species have evolved together over millions of years. We must consider how our health is dependent upon the establishment and maintenance of a healthy human microbiome, and that this microbiome plays a vital role in keeping us healthy and disease free. If there was ever work that should reduce the fear the typical layman has of microorganisms, it should be the HMP.

Finally, we must be cognizant that what makes the results of the HMP strikingly different from previous assessments of human microflora is the analytical approach taken in the study. The HMP was the first comprehensive effort to apply modern molecular biological methods to the assessment of human/microbiological

interaction. The result was the discovery that the human flora, in terms of sheer numbers of bacterial species and total organism number, was more diverse than previously imagined. Over the past few years, reports have emerged that the world's potable water supplies contained hundreds of thousands more organisms than previously thought to be present, representing a signal of microbial viability than had not previously been recognized. The common denominator in these studies is the use of molecular biological methods rather than traditional growth-based methods reporting results in CFU. This is no different scientifically from astronomers and astrophysicists finding more celestial objects using the Hubble telescope than they were able to perceive using earth-based optics. Science waits for no man and abides by no human-invented regulation.

The finding that the human organism is colonized by a larger number of organisms does not equate to greater risk, it only equates to greater knowledge, which must be applied wisely. As molecular microbiological methods are more widely used, we are likely to have other surprises, but this does not require us to fear new methods or to shy away from their implementation, it merely requires us to understand that if our processes haven't changed, then patient risk must not have changed either. We haven't uncovered new objective dangers, because the nature of humans and their environment hasn't changed, only our knowledge of it has changed.

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Will Advances in Controlled Release Open Up New Drug Delivery Opportunities?

Adeline Siew, PhD

Emerging controlled-release technologies could lead to more effective therapies in the near future.

Controlled-release formulations may be more challenging to formulate than traditional dosage forms, but they offer a number of distinct advantages, including:

- Improved bioavailability
- Prolonged duration of therapeutic effect
- Reduced adverse reactions due to the maintenance of drug concentration within a desired range without exposing the patient to potentially toxic drug levels
- Better patient compliance, as a result of reduced dosing frequency, especially in cases of chronic diseases where complex drug regimens are involved.

For pharmaceutical companies, controlled-release formulations are developed as part of a lifecycle management strategy to differentiate their products from generic drug competition and

thereby extend market exclusivity. Technologies for controlled-release drug delivery continue to advance, driven by increasing demand. This article looks at some of new developments in the field.

IntelliCap, an electronic drug delivery and monitoring device

Medimetrics' electronic controlled-release oral drug-delivery system, IntelliCap, is a drug-delivery and monitoring device that consists of a cap containing the drug reservoir and a body containing a microcomputer and wireless data exchange unit (1, 2). The ingestible, single-use electronic device has built-in functionalities such as pH and temperature sensors. IntelliCap can be programmed to the desired drug release profile, and the drug can be targeted to specified regions of the gastrointestinal tract. An interesting feature is its

ability to achieve real-time control and adjustment of drug delivery while the capsule is in the body (1, 2).

IntelliCap can also be used for quick *in-vivo* assessment of pharmacokinetics and gastrointestinal transit times of controlled-release formulations. For example, the device has been used to quantify regional drug absorption in human gastrointestinal tract. In this study (3), an IntelliCap system containing diltiazem (i.e., the model drug) was programmed to have the same drug release profile (based on *in-vitro* dissolution data) as the commercial extended-release formulation of diltiazem, marketed by Mylan Pharmaceuticals. Results showed that the mean pharmacokinetic data of both formulations were similar. However, a higher peak plasma concentration (C_{max}) and longer time to reach peak plasma concentration (T_{max}) were observed with the commercial formulation. This variation was due to the different dosage forms. IntelliCap is a monolithic unit while the commercial formulation is a multiparticulate system, which is known to take longer to travel through the small intestine, accounting for the longer T_{max} and higher C_{max} (3).

Chronocort, controlled release that mimics the circadian rhythm

Chronocort, developed by Diurnal, a spin-out company from the University of Sheffield, United Kingdom, is a controlled-release, oral formulation of hydrocortisone (cortisol) for the treatment of adrenal insufficiency and congenital adrenal hyperplasia. The multiparticulate formulation has been designed to release the hormone in a manner that mimics the body's natural circadian rhythm (4).

Cortisol, more often known as the "stress hormone," is a steroid hormone secreted by the adrenal gland. Cortisol levels in the body follow a circadian rhythm that is regulated by the main circadian oscillator (pacemaker) in the suprachiasmatic nucleus, located in the hypothalamus. In healthy individuals, cortisol levels build up overnight, reaching a peak in the morn-

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ing. They slowly decline throughout the day, falling to low or undetectable levels towards midnight (5). The management of adrenal insufficiency has always been a challenge because hydrocortisone has a short plasma half life and patients taking the hormone will only achieve peak cortisol levels one hour after consuming the tablet. Furthermore, it is difficult to replicate physiological cortisol release with immediate-release hydrocortisone tablets.

A Phase II study of Chronocort in 16 adults with congenital adrenal hyperplasia showed positive results in demonstrating that Diurnal's controlled-release formulation provided cortisol levels that mimic the circadian rhythm observed in healthy people (6, 7). Patients treated with Chronocort woke up with normal cortisol levels in the morning, and their cortisol profiles matched physiologic cortisol secretion.

A microchip-based implant for pre-programmed dosing schedules

Microchips Biotech has developed a proprietary microchip-based implant that can store and release precise doses of a drug on-demand or at scheduled intervals for up to 16 years (8, 9). The physician first places the implant under the skin of the patient, using a simple procedure performed under local anesthesia. Once implanted, the device can be activated or deactivated through wireless signals by the physician or patient. The physician can also wirelessly tailor the frequency and dose of the drug to suit the individual patient's needs without having to remove the implant.

The microchip-based implant contains 200 micro-reservoirs in small hermetically sealed compartments, each storing up to 1 mg of drug (9). Activation by a wireless signal triggers drug release from the micro-reservoirs according to a pre-programmed dosing schedule. The implant can be built with sensors that release the drug in response to physiological or metabolic changes in the patients. There are control electronics within the implant, such as radio frequency communications, a clock for accurate timing of drug release, a custom circuitry that

is electrically connected to individual doses to allow independent dispensing of each dose at any time or in any sequence, and a microcontroller that provides control of all necessary functions. Instructions from an external device (which can be a cell phone, a tablet, or a custom transceiver connected to a computer) are communicated to the implant through radio frequency. The distance between the external device and the body with the implant must be within 3 m for communication to be established (10).

The technology is being explored as a potential treatment for diabetes and osteoporosis as well as female contraception. The first human trial (11) was conducted in women with osteoporosis. The microchip-based implant was used to deliver teriparatide, an approved anabolic osteoporosis treatment that requires daily subcutaneous injections. The device was implanted in eight osteoporotic postmenopausal women for four months, with the microchip programmed to release the drug, once daily, in escalating doses, for up to 20 days (11). Pharmacokinetic evaluation demonstrated that the drug release profile of the implant was comparable to that of the standard daily injections of teriparatide, but with less variation in pharmacokinetic parameters because of the consistent dosing intervals delivered by the implant. Moreover, bone marker evaluation showed increased bone formation in the study subjects. Changes in serum calcium, N-terminal propeptide of type I procollagen (PINP, marker for bone formation), and C-terminal telopeptide of type I collagen (CTX, marker for bone resorption), resulting from the implant, were found to be qualitatively and quantitatively similar to those observed with daily subcutaneous injections of teriparatide. No adverse reactions due to the implant were reported (11).

Wearable injectors

Enable Injections is developing wearable bolus injectors for the delivery of high-viscosity and high-volume drugs in development (12, 13). The technology is currently available for investigational purposes and is particularly applicable

for large molecules such as biologics, which often present challenges in drug delivery due to their high-viscosity, high-volume formulations. As the system is fully automated, patients can self-administer their medication. The injector has the capacity to deliver payloads of up to 20 mL to the subcutaneous tissue over a time frame that can range from minutes to hours. The system is designed to offer patients a safe, simple, and discrete device that provides a controlled and comfortable flow of drug at a rate that adapts to the wearer. Operation is simple, requiring only one push of a button. A "pause function" has been incorporated into the injector, allowing users to stop the injection at any time.

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An Orthogonal Approach to Biosimilarity

Randi Hernandez

In this article, industry experts discuss critical analyses for demonstrating biosimilarity.

There is a resounding consensus among industry experts that multiple bioequivalency approaches and orthogonal methods will be required for the assessment of biosimilarity. *Pharmaceutical Technology* spoke to experts Daniel Galbraith, PhD, chief scientific officer, BioOutsource; Michael Sadick, PhD, senior manager, large molecule analytical chemistry, Catalent Pharma Solutions; Gary Chambers, business manager for biopharma labs, Europe, SGS Life Science Services; Glenn Petrie, PhD, senior scientific advisor, ABC Laboratories; and Joerg Windisch, chief scientific officer, Sandoz to learn more about best practices for analytical testing of biosimilars.

Current testing methods

PharmTech: Which methods of analysis to demonstrate biosimilarity are most effective?

Galbraith (BioOutsource): The key assays for each molecule are those that mimic the biological activity of the drug *in vivo* and are shown to be sufficiently sensitive to specific differences

in the physicochemical structure. The reason being is that these are the ones that are most likely to fail in clinical trials. These are mainly the bioassays using specific target cells. The ones that are used the most are the ligand-binding assays; these are used as markers or indicators for the biological functional activity. Ligand-binding assays are fast and cheap to do, so they are used as screening assays on a large number of samples.

Sadick (Catalent): As far as I am aware, there is no one, or even a few, type(s) of assessment(s) that can verify biosimilarity. It really will require an orthogonal approach that combines physicochemical and functional analyses. Even for functional assays, there ought to be an orthogonal array of cell-based and ELISA-based potency assessments, as well as binding kinetic determinations. The array of functional assays may be winnowed with time as more is known.

Chambers (SGS Life Science Services): In our experience, orthogonality is the key approach because one test may not reflect subtle differences between an innovator and a biosimilar. For

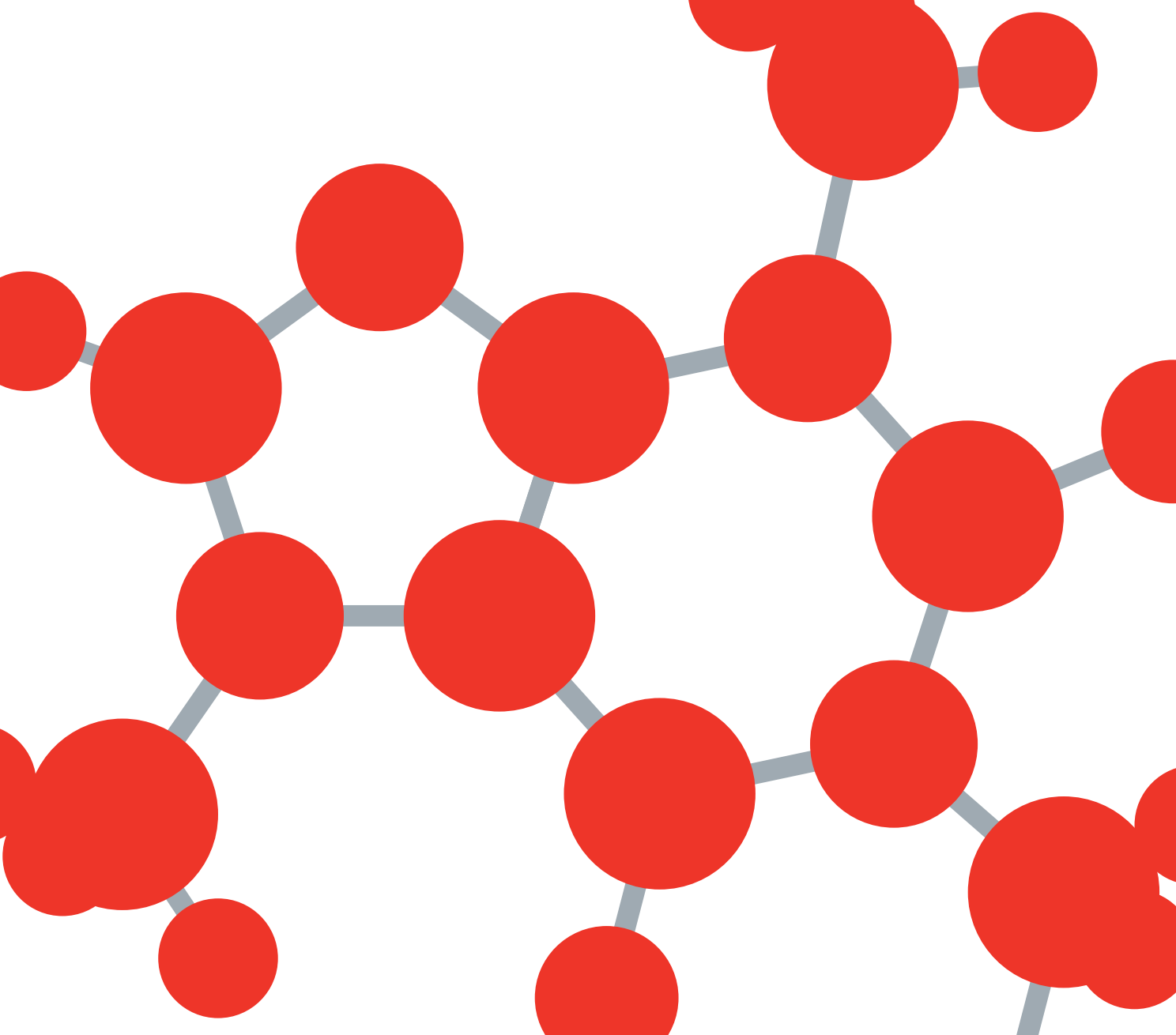
example, the paired analysis of Fourier transform infrared spectroscopy (FTIR) and circular dichroism (CD) will provide measurement of secondary structure. While both measure alpha helices and beta-sheets, FTIR is stronger with beta-sheets, while CD is better with alpha helices. This approach also applies to aggregation where size-exclusion chromatography–multi-angle laser light scattering (SEC–MALS) and sedimentation velocity analytical ultracentrifugation (SV–AUC) are utilized. Any variations can then be further investigated using characterization methods such as peptide map tandem mass spectrometry (PMAP–MS/MS) and electrospray ionization mass spectrometry (ESI–MS).

Petrie (ABC Laboratories): The critical analysis for demonstrating biosimilarity is the bioassay. Binding, chromatographic, and electrophoretic analyses provide useful and required data, but the activity assay is the only one that truly reflects bioequivalence.

Windisch (Sandoz): There is no single method that will be the most important one. At the end of the day, you always have to account for the different structural components. You need to start with the primary structure, the amino acid sequence, the higher-order structure, the folding, the heterogeneity, the glycosylation, the impurities, and then you have to move from structural characterization to characterizing all of the different functionalities of the molecule. It's really an all-encompassing exercise. There are really two principles here: one of them is redundancy, and the second thing is orthogonality. Overall, you could end up with anywhere between 50–60 methods to analyze structure—the chemical analytics—and another probably 15 methods to test function.

PharmTech: What can binding studies tell investigators about similarity between product candidates?

Sadick (Catalent): ELISA, or any other type of quantitative binding assay (whether it be designed as a content assay or as a potency assay)



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will define the steady state binding characteristics of the molecule. If the molecule is a monoclonal antibody (mAb), then an array of binding assays should be used to assess both CDR/ligand interaction and Fc/Fc receptor interaction. Even more detailed information can be derived from binding kinetics testing, using either surface plasmon resonance (SPR; e.g., Biacore) or bio-layer interferometry (BLI, e.g., Octet).

Chambers (SGS Life Science Services): Once you have established the acceptable variation, these can tell you if the binding between candidates is similar. If it is not, the data can be compared to secondary/tertiary structure analysis methods to assess whether the differences can be attributed to a conformational change in the candidate.

Petrie (ABC Laboratories): Typical ELISA or electrochemiluminescent assays can provide concentration data and a relative tool for comparison of binding curves. True binding characteristics require the use of surface plasmon resonance techniques which provide the association/disassociation rates and binding constant. This allows quantitative comparison of the binding characteristics of product candidates and the innovator product.

Galbraith (BioOutsource): Binding studies are an important first step in the biological or functional characterization of a molecule. Simple binding studies can tell us if the molecule binds and how tightly. More in-depth analysis such as SPR will inform on the kinetics of binding and disassociation, which is key in showing the same modes of action.

PharmTech: Has the demand for biosimilarity testing services increased in the past few years?

Chambers (SGS Life Science Services): The demand has increased, with more clients requesting development partnerships rather than just testing support.

Petrie (ABC Laboratories): We have had a definite uptick in the number of requests for analysis of biosimilars. Based on the number of biopharmaceuticals

going off patent and the FDA's clarification of the requirements for biosimilarity, I see continued growth for the foreseeable future.

Galbraith (BioOutsource): We have seen an exponential increase in biosimilarity testing for two reasons: There are more companies involved in biosimilar development today, and there are more molecules being targeted. I would estimate that the industry has doubled every year for the past four years.

Sadick (Catalent): We are beginning to see a marked increase of interest, by current and potential clients, for provision of biosimilarity testing strategies and services.

PharmTech: Is the most practical way to assess bioequivalency to use one assay for both the originator and follow-on biologic?

Petrie (ABC Laboratories): While difficult, the preferred method for comparison of the bioequivalent and innovator drugs is assay by the identical method. Bioassays and ELISAs already have a high degree of variability. Introduction of a second method further complicates the situation and makes comparison of the data extremely difficult. Justification for the use of a second assay and its validity produces additional regulatory challenges.

Galbraith (BioOutsource): If there were one assay that could cover all of the potential functions a monoclonal antibody is able to perform, this would be ideal. We could then assess the innovator and biosimilar alongside and get an idea of the level of similarity. However, because the human body is a complicated system, we cannot replicate this in the lab and therefore, a single assay is not possible. In the lab we need to assess each function a monoclonal antibody performs in different assays to build up a full picture of all of these activities.

Sadick (Catalent): Not necessarily. Variability will be based upon the precision, accuracy, and robustness of each of the tests that are combined orthogonally to assess biosimilarity.

Chambers (SGS Life Science Services): I would say we are being pushed to look at multiple bioequivalency approaches to support similarity assessment.

PharmTech: Is it possible for a follow-on biologic to be truly equivalent, but test results do not validate biosimilarity?

Galbraith (BioOutsource): It is conceivable that some minor effector functions do not show similarity but the overall conclusion is that this will not affect the clinical efficacy of the drug and hence, a conclusion of similarity will be made.

Chambers (SGS Life Science Services): Yes, a biosimilar may achieve equivalent clinical results, but analytically we may see variations. These differences may not impact the product binding and so do not impact activity.

Petrie (ABC Laboratories): There is the potential that a biosimilar could have the same clinical results as the innovator without meeting all the analytical requirements. Bioassays and binding assays have enough variability that they could fail bioequivalent criteria. However, convincing regulators that despite these failures the drug is equivalent presents a considerable obstacle to approval.

PharmTech: What are some of the potential barriers to obtaining sufficient amounts of reference product from originator companies for biosimilarity testing?

Sadick (Catalent): Under the current system, it can be quite difficult to obtain sufficient amounts and variety of originator material to provide a truly appropriate baseline for comparison. Costs can be very steep to obtain originator material, and not all originators make their material available, despite being paid for their medications. It usually requires a dedicated group within the company (the biosimilar company and/or the contract testing company) to facilitate obtaining originator material.

Chambers (SGS Life Science Services): One barrier is ensuring that material obtained remains within the expiry date



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prior to testing. Additionally, obtaining material around the same time as its manufacturing date to put on stability studies is another potential barrier.

Galbraith (BioOutsource): It can be challenging to obtain sufficient batches of product. At BioOutsource, we link into a global supply network and have good access to batches, but with some drugs, there is a global limit to supply of innovator drugs.

Presenting biosimilar data to regulatory authorities

PharmTech: How should biosimilarity results be presented to FDA?

Windisch (Sandoz): We have gained quite a bit of experience through our recent filing. FDA wants to look at the molecule and its attributes from the perspective of the clinical relevance of all of these attributes. The agency wants manufacturers to take a complete look at the molecule, look at all of its structural components, make a systematic evaluation as to the clinical relevance of the different parts of the molecules, and then it wants them to do a criticality assessment and rank them. Going from that criticality evaluation, the agency wants manufacturers to focus on those differences that matter or even potentially matter and provide ample analytical and functional data on each one of them.

Galbraith (BioOutsource): FDA is interested in the totality of evidence, essentially taking all of the information and summing it up into a statement that defends the claim of similarity. Each assay used in this assessment needs to demonstrate its ability to identify where changes in the molecule are key to clinical efficacy.

Chambers (SGS Life Science Services): The format should be tabulated with innovator data against biosimilar data. To keep this simple, it is better to have one column for innovator and biosimilar and provide ranges for each parameter tested. In addition, in the same table, a manufacturer should include a column for variation. This table should include specifications that include experimen-

tally determined method and process variation, allowing an assessment of similarity to be made.

PharmTech: What additional tests will likely be required to demonstrate interchangeability?

Galbraith (BioOutsource): Interchangeability is really more of a clinical assessment and is not likely to be answered by laboratory analytics.

Chambers (SGS Life Science Services): To demonstrate comparable quality, safety, and efficacy, following batch release/stability testing and full ICH Q6B characterization, forced degradation studies should also be included. Ultimately, clinical trial data will also be required.

Petrie (ABC Laboratories): While not providing the critical data supplied by binding studies and bioassays, biosimilars require the complete set of analytical techniques required for any biopharmaceutical. This may include high-pressure liquid chromatography (HPLC), SEC, liquid chromatography-tandem mass spectrometry (LC-MS/MS), peptide map, capillary electrophoresis (CE), and micro-flow imaging (MFI).

Windisch (Sandoz): Manufacturers already have to provide complete characterization for a biosimilar. What you could assume is that FDA would look at any potential small differences—such as in the heterogeneity—somewhat more critically when it comes to interchangeability.

Testing complex structures

PharmTech: What specific challenges exist when it comes to testing the biosimilarity of mAbs?

Sadick (Catalent): The challenges, as I see them, are that there are multiple levels at which bio-dissimilarity could impact a monoclonal antibody. Certainly, there is the risk that any change in amino acid sequence, glycosylation, secondary, tertiary, or quaternary structure could result in a change in immunogenicity. Additionally, any of those same alterations could impact complementarity determining region/

ligand interaction, Fc/Fc receptor interaction, or both.

Galbraith (BioOutsource): The challenge of testing mAbs is accurately defining the acceptable range of the critical quality attributes. Each batch of the originator drug can vary, and it is possible that changes may be made to the manufacturing process that could result in a change of the profile of the quality attributes. Attempting to define an acceptable range for your biosimilar molecule within these potentially moving goalposts can be challenging.

Chambers (SGS Life Science Services): Establishing expected variation is a challenge. This is often determined using a statistically suitable number of innovator batches and this also poses sourcing issues, as all material tested should be within the expiry date. Sourcing sufficient material often becomes a rate-limiting factor.

Petrie (ABC Laboratories): Establishing the biosimilarity of mAbs is challenging due to the complexity of their structure. Multiple subunits, disulfide linkages, post-translational modifications, and glycosylation require a myriad of analytical techniques. The advent of powerful mass spectroscopic techniques has simplified these analyses to an extent, but an enormous amount of effort is still required.

Windisch (Sandoz): With monoclonal antibodies, you will often hear they are so much more challenging than some of the other molecules that have already been done; this is only partially true. A monoclonal antibody is complex in that it is large, but in other ways, it's also a fairly robust and relatively simple molecule. The biggest challenge is probably understanding the structural-functional association as it relates to the activity of an antibody.

In most cases, the binding is not so much of an issue, because typically the binding site doesn't have sugars and is not glycosylated. What are more challenging are the effector functions, which are in the Fc fragments. These

are influenced by glycosylation and include the recruitment of the cellular immune system—the antibody-dependent cellular cytotoxicity—and the recruitment of the molecular immune system—or the complement-dependent cytotoxicity. Both of these can be influenced by the glycans, by the sugars in its Fc fragment, and one needs to fully understand the structures there and how they influence biological activities. This is really an interplay between doing cell line and process development work and then analyzing the variant that you get both from a structural and a functional perspective.

PharmTech: Will biosimilar products that incorporate fusion proteins or bispecific antibodies be more difficult to test?

Galbraith (BioOutsource): Enbrel (etanercept) is a fusion protein and is currently undergoing testing; this has not presented any difficulties thus far.

Windisch (Sandoz): Fusion proteins such as etanercept can be more challenging to test and can be more complex in structure (i.e., they can be highly glycosylated). On the other hand, you have to look at each molecule individually. You can have a more complex structure, but not all of the molecular attributes are clinically relevant. The challenge is developing your cell line in your process to actually create a close match of the molecule. While it can be more challenging to test fusion proteins, for bispecific antibodies, there is no difference from a normal antibody.

Chambers (SGS Life Science Services): Yes. In some cases, these are highly potent and require testing at low-level concentrations for which standard mAb testing methods are not designed. Additional tests will also be required to account for differences in degradation pathways.

Petrie (ABC Laboratories): Fusion proteins, ADCs, and bispecific antibodies present the same challenges as mAbs due to their complexity. Characterization and analysis are required for not

only the drug substance, but the linker and the fusion component, adding the complications to the demonstration of biosimilarity.

In Vivo vs. In Vitro

PharmTech: Does using a biologically derived technique as an assessment method complicate testing?

Petrie (ABC Laboratories): Any bioassay presents special challenges related to cell lines, cell culture, laboratory technique, etc. These challenges are only multiplied for biosimilars. Small differences in the method, even those improving the method, may differentially affect the results generated for the biosimilar and innovator drug.

Galbraith (BioOutsource): Biological products are much more complicated and variable than traditional small-molecule products; this is a simple fact. The reason for this is that we use living cells or we use materials harvested from living systems such as blood or serum. These materials do not lend themselves to consistency, and therefore, the assays require much more control and larger datasets. The upside is that these assays will show potency, something that chemistry analysis is not able to do.

Sadick (Catalent): The *in-vitro* biological activity of a therapeutic molecule is not often completely biomimetic to the therapeutic action of that molecule *in vivo*. Thus, differences in *in-vitro* activity cannot always be directly related to the *in-vivo* activity (in a 1:1 fashion). The *in-vitro* test, however, should be reflective of the molecule's therapeutic mechanism of action. Differences in *in-vitro* activity should accurately predict differences in *in-vivo* activity, providing vital information.

PharmTech: Can results of *in-vitro* tests be predictive of biological activity *in vivo*?

Galbraith (BioOutsource): There is always the caveat that *in vitro* cannot truly replicate the *in-vivo* world. Activity we see in a test-tube can sometimes be due to the environment. These tests, however, have moved on significantly

even in the past couple of years and are significantly better at estimating the *in-vivo* activity.

Sadick (Catalent): The orthogonal combination of physicochemical and biological analyses of a biosimilar molecule is not proof positive of the biosimilarity of that molecule *in vivo*. However, a combination of *in-vitro* tests should be reflective of a molecule's critical attributes. Results from these tests should hopefully minimize the extent of any clinical studies needed for verification of biosimilarity, safety, and efficacy.

Petrie (ABC Laboratories): *In-vitro* analysis can confirm that the biopharmaceutical has the proper three-dimensional structure, binding characteristics, and mode of action. These assays, however, cannot predict activity *in vivo* due to the effects of bioavailability, clearance rates, etc.

PharmTech: How is the immunogenicity potential of a biosimilar candidate assessed? What testing methods are typically used?

Galbraith (BioOutsource): Immunogenicity can be assessed *in vitro*—the cytokine storm assay has been applied to some products. More often, however, this is left to the clinical trials, where anti-drug antibodies are assessed in a screen of the patients.

Petrie (ABC Laboratories): Immunogenicity for the innovator and biosimilars are determined identically. ADAs are determined in Phase I and II by means of increasingly specific ELISA or ECL assays.

Sadick (Catalent): While some predictive *in-silico* testing (of amino acid sequences and glycosylation patterns) may be performed, and even may be somewhat useful, these predictive studies usually only minimally reflect the *in-vivo* reality of immunogenicity. That, unfortunately, leaves preclinical assessment of immunogenicity, which, in itself, is not always predictive of immunogenicity in humans. Continued immunogenicity assessment will likely be required in human recipients for a while. **PT**

Predicting Meaningful Process Performance

Mark Mitchell

Process design experimental data and risk assessments are used to predict expected process performance and establish process performance qualification acceptance criteria.

FDA's current process validation guidance (1) has presented an implementation challenge for many pharmaceutical organizations since it was published in 2011. This revision of the original 1987 process validation guidance became necessary due to concerns about poor quality drugs on the market from supposedly validated processes and from drug shortages caused by unreliable commercial processes producing low quality products that could not meet release specifications. The 2011 *Guidance for Industry, Process Validation: General Principles and Practices* document (1) imple-

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ments a product lifecycle concept that effectively aligns with and encourages concepts from guidances published by the International Conference on Harmonization (ICH), namely ICH Q8 *Pharmaceutical Development* (2), ICH Q9 *Quality Risk Management* (3), and ICH Q10 *Pharmaceutical Quality System* (4).

Per ICH Q8, the aim of pharmaceutical development is to design a quality product and design its manufacturing process to consistently deliver that quality product. This approach is because quality cannot be tested into products; quality must be built in by design. This concept of quality by design is hardly revolutionary. Design controls for medical devices specifically address the importance of how upfront design impacts

the quality performance of the device in the hands of a patient. In another example, aseptic processing does not depend solely on the use of end-point sterility testing, but on the design of equipment and facilities and the control of processes and personnel. Any validation engineer realizes quickly that a piece of equipment that is not designed for qualification is difficult, if not impossible, to qualify. Drug product manufacturing processes are no different; a process must be designed from the start to produce quality product.

The first stage of FDA's process validation guidance is process design, and its purpose is to define a process and its necessary controls to reliably produce a quality product (i.e., a process control strategy). The second stage is process qualification; its purpose is to confirm that the process as designed (in Stage 1) with its defined process control strategy will not only produce quality product for the duration of the qualification, but also reproducibly continue to do so into the future. This article explores how to use data generated during process design to establish meaningful and statistically justifiable acceptance criteria for the process performance qualification (PPQ) in Stage 2.

Specifications and acceptance criteria

For users of the process validation guidance, the focus has been primarily on the justification of the number of lots (since three lots may or may not be sufficient) and how to implement enhanced sampling with "statistical confidence of quality of both within a batch and between batches (1)." Critical process parameters (CPP) no longer are required to be tested to the extremes of their operating ranges during PPQ; those limits have been justified through data or risk assessment performed during process design. Less effort has been put into determination of well-defined acceptance criteria for PPQ. In most cases, the acceptance criteria are the end-product release specification limits and the in-process control limits. PPQ may have more

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lots; PPQ definitely has more samples to be tested. For these cases, however, process qualification only requires that each PPQ lot pass its end product release specifications and in-process controls limits with no additional acceptance criteria.

There are several flaws with this approach. The first is a “goal post” mentality. As long as the product is within the specification limits (the goal posts), quality is good; if the product is outside the limits, quality is bad. For those trained in the concepts of Six Sigma and Lean Manufacturing, the loss of quality is best described as a Taguchi Loss Function where the quality gradually decreases (or the loss of quality increases) as the result for the quality attribute moves away from its intended target. The best quality is found as far from the specification limit as possible (i.e., as close to the target value as possible). Product near the specification limit is not “good” but rather “barely acceptable.” The goal should be to design processes that can achieve the best quality for customers and patients.

The second flaw comes from understanding the statistical relationship between a population (the lot, or groups of lots) and a sample from that population (the material tested). One can test a group of samples and determine a sample mean (the average of the samples tested) and statistically infer the value of the population mean (the true mean of the lot, which is unknown). When the sample mean is at the edge but still within the limit of the specification, the lot is accepted. Sample variation (and testing variation) can occur, however, so there is a likelihood that a second sampling could, in fact, be outside of the specification. In fact, this case is only unlikely when the lot has been determined to be extremely uniform.

The third flaw comes from believing that a quality product (passing product specifications for the number of PPQ lots) means a good process. Certainly, it is necessary for PPQ lots to produce quality product (pass specifications). Bad processes, however, also can make good product; the difference is

that bad processes are unreliable and unpredictable. Product specifications are designed to judge the quality, safety, efficacy, identity, and strength of the product. Specifications define what the patient needs and are thus described as “the voice of the customer.” Processes have to be judged by how predictably they will produce that quality product. Statistical concepts such as statistical control (predictable data that are normally distributed) and process capability (measurements of process mean and variation relative to specification limits) are described as “the voice of the process.” To assess the process as well as the product during PPQ, acceptance criteria, in addition to specification limits, are needed.

Linking Stage 1 and Stage 2

The output of process design (Stage 1) is a defined commercial manufacturing process with a process control strategy to ensure product quality. Process qualification (Stage 2) is the qualification of the process by demonstrating that the process control strategy can reproducibly produce quality product. Per the FDA process validation guidance (1), Stage 2 will “confirm the process design” and ensure that the process “performs as expected.” For a process to perform as expected, it needs to be reproducible and therefore, predictable. To complicate assessing predictability, manufacturing processes are rarely deterministic. In a deterministic process, all process inputs are fixed so that an exact process output can be calculated. Real-life processes are probabilistic and are affected by numerous random factors. Even so, when a process is in statistical control, the output of the process will have predictable data distributions with the normal distribution being the most common.

The primary work in the process design stage is to understand the relationships between CPPs (and critical material attributes [CMAs]) and the outputs of the process (the quality attributes). These relationships may be derived from design space models produced using design of experiments (DOE),

first principles, or prior knowledge of existing unit operations and process equipment. The collection and statistical analysis of data from process design should consider the eventual need of using these data to support PPQ acceptance criteria.

Acceptance criteria using a prediction model

In the first example, a solid oral-dosage form is produced by applying an extended release coating with a fluidized spray coater. One of the critical quality attributes (CQA) for the process is the % dissolution at 4 h. The specification for this attribute is 20% to 40% using the United States Pharmacopeial dissolution method. Many of the process parameters for the spray coating (such as air temperature, dew point temperature, air flow, coating solution flow rate, etc.) have either been determined to be non-critical process parameters or are fixed set points, which are well-controlled with little measured variation. A series of design of experiments at small scale with verification at commercial scale were conducted.

Using the first principles of mass balance of the dried coating solution on the pellets and the mechanisms of dissolution, it is expected that the rate of dissolution is driven by the surface area and coating thickness of the final pellet. Statistical analysis of the experimental design confirmed that the process input of the average diameter of the uncoated pellet was statistically significant. Therefore, the average diameter of the uncoated pellet is a CMA for the spray-coating process. Note that this parameter can also be considered as an output, or in-process control, of the previous process step.

Figure 1 shows the combined results of several process design experiments where various uncoated particle sizes were used. A simple linear model is fitted to relate the particle size to the resulting dissolution of the uncoated particle. Despite some variability about the model, the R-squared value of 83.8% indicates that this material

attribute dominates the resulting dissolution over any other factors.

The model (solid black line) is the best fit, on average. However, the “true” model line more probably lies between the 95% confidence interval lines (dashed red lines). This is still where the dissolution results will lie, on average, for a given particle size. If we wish to predict what the dissolution result for any given run might be, we use the 95% prediction interval lines (dotted green lines). Therefore, this model predicts if an uncoated average particle size of 436 μm is used, the dissolution result should be between 22 and 29 approximately 95% of the time. If the process control strategy is properly applied, this prediction model should hold for not only PPQ lots, but for all future lots produced with this control strategy. If this model breaks down, it indicates either that the process control has failed or an unexpected event has occurred.

Using this model’s prediction intervals as acceptance criteria for dissolution in the PPQ lots, confirms that the commercial process is following a statistical prediction for a CQA. Using the dissolution specification limits (20–40%) as the sole acceptance criteria, essentially ignores the process knowledge and prediction model developed during process design, and could lead to an unpredictable process being qualified.

This example used a simple linear model of one-factor, but the same approach can be applied to more complex multi-factor models as long as the variability of individual lots around the model best-fit line is taken into account.

Figure 1: Linear prediction model for dissolution at 4 h (CI = confidence interval, PI = prediction interval, R-Sq = R-squared).

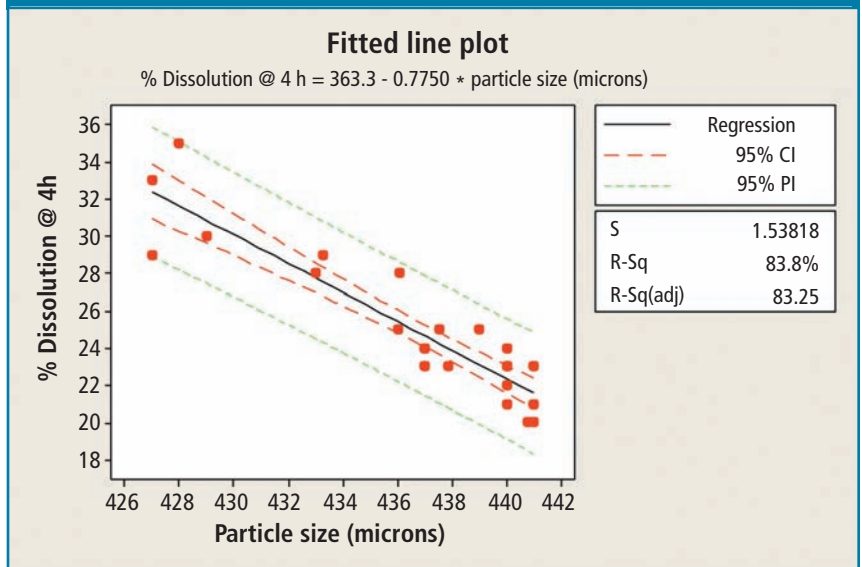
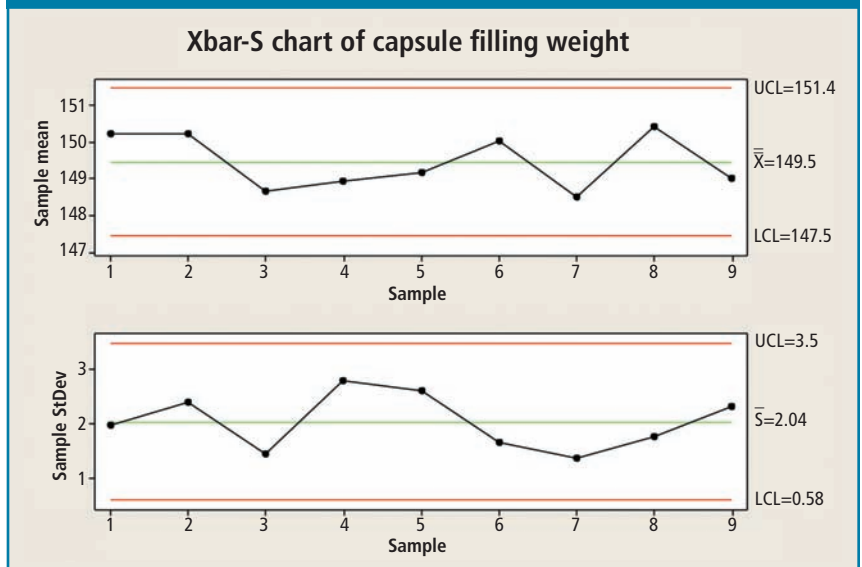


Figure 2: Capsule filling weight X-bar and S charts (UCL/LCL = upper/lower control limit, \bar{X} = sample average, $\bar{\bar{X}}$ = average of sample averages, StDev = standard deviation, \bar{S} = average of sample standard deviations).



Acceptance criteria using process capability

As discussed, a process that is in statistical control will produce a predictable output, which frequently is shown as a normal distribution. This distribution is compared to the specification limits to calculate a process capability index (Cpk). A higher capability index indicates a lower likelihood of producing out-of-specification product. Statistical

control is a prerequisite for calculating process capability, because processes that are not in control are not predictable for future performance.

In this example, a capsule filling process is assessed for the in-process control of filling weight, which is a determining factor for the CQA content uniformity. The specification for the filled capsule weight is a target of 150 mg \pm 12 mg. Capsule filling weight was

collected during Stage 1 small-scale clinical builds and during filler speed runs performed as part of the performance qualification of the capsule filler. Consistent filling performance was confirmed over several runs.

Figure 2 and **Figure 3** report the data collected from a full-scale run using the worst-case filling speed with 10 samples collected every 60 minutes. **Figure 2** shows the X-bar (mean of samples at each time-

Figure 3: Capsule filling weight capability (USL/LSL = upper/lower specification limit, N = number of samples, StDev = standard deviation, CL = 95% confidence limit, PPU/PPL = upper/lower overall process capability, Ppk = overall process capability [minimum of PPU and PPL]).

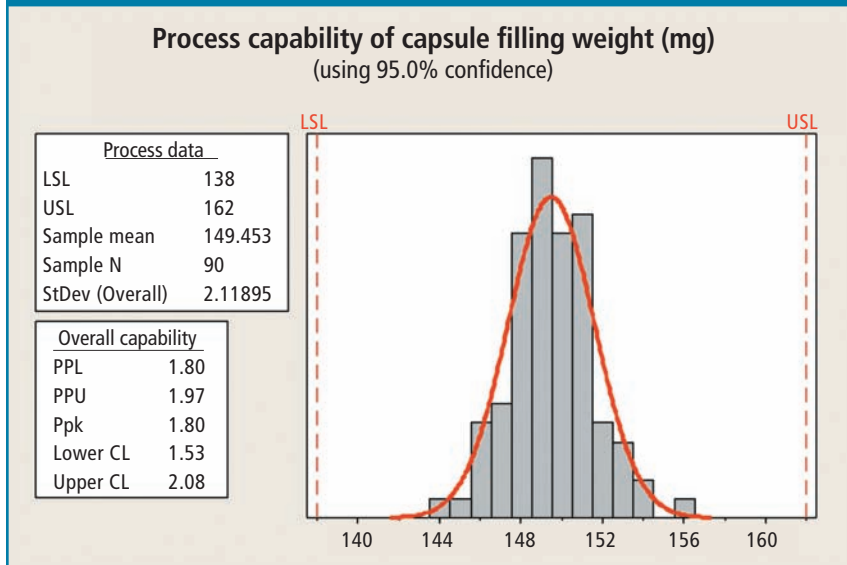
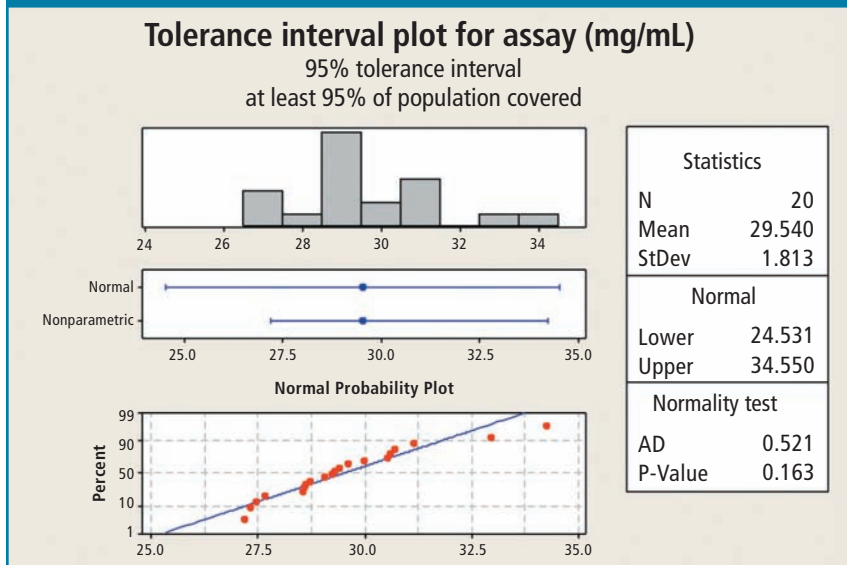


Figure 4: Tolerance interval for assay for 95% confidence/95% coverage (N = number of samples, StDev = standard deviation, AD = Anderson-Darling statistic)



point) and the S (standard deviation of samples at each timepoint) control charts. These control charts indicate good statistical control with no trends, shifts, or points beyond the upper and lower control limits (UCL and LCL). Because the process is in statistical control, the process capability index can be calculated.

Figure 3 is a histogram, which graphically displays the data distribution

relative to the specification limits. As expected, the data are a good fit to a normal distribution. Capability indices can be either calculated as a Cpk (assumes no shift or drifts between subgroups) or as a process performance capability index (Ppk) (based on the overall distribution of the data). The Ppk, a less ideal case, is calculated in this example. The Ppk is 1.80, but this

is based on the sample standard deviation. To obtain a population standard deviation for calculating capability, the 95% confidence limits for the Ppk is calculated as 1.53 to 2.08. Using the lower confidence limit is especially useful when the amount of data to calculate the capability is limited.

For PPQ runs, an assessment of the statistical control charts for capsule filling weight and acceptance criteria of not less than the lower 95% confidence limit of 1.53 can be used as additional acceptance criteria. This acceptance criteria will ensure that the filling is predictable and the process performs as predicted by earlier studies. Additionally, there is now a very low statistical probability of filled capsules near the specification limits, if any. If only the specification limits of 138–162 mg had been used, no assessment of statistical control could be done and no prediction of future performance could be calculated.

Acceptance criteria using statistical tolerance intervals

The final example examines the use of statistical tolerance intervals. A tolerance interval defines the limits that a defined proportion of the distribution (called the coverage) will fall within to a defined confidence level. Tolerance intervals do not depend on the value of the mean or the standard deviation of the distribution, only the proportion. Tolerance intervals can be calculated with an expectation of a normal distribution or can be nonparametric with no assumptions about the distribution of the data.

In this example, the data for the CQA, assay, are collected over five process design experimental runs with four samples from each run. Runs representative of the typical conditions (i.e., not extreme conditions) for parameters that impact assay are selected. The specification limits for assay are 20–40 mg/mL. The tolerance interval is constructed using multiple Stage 1 lots with multiple samples from each lot, to capture both within lot and lot-to-lot variation. An analysis of

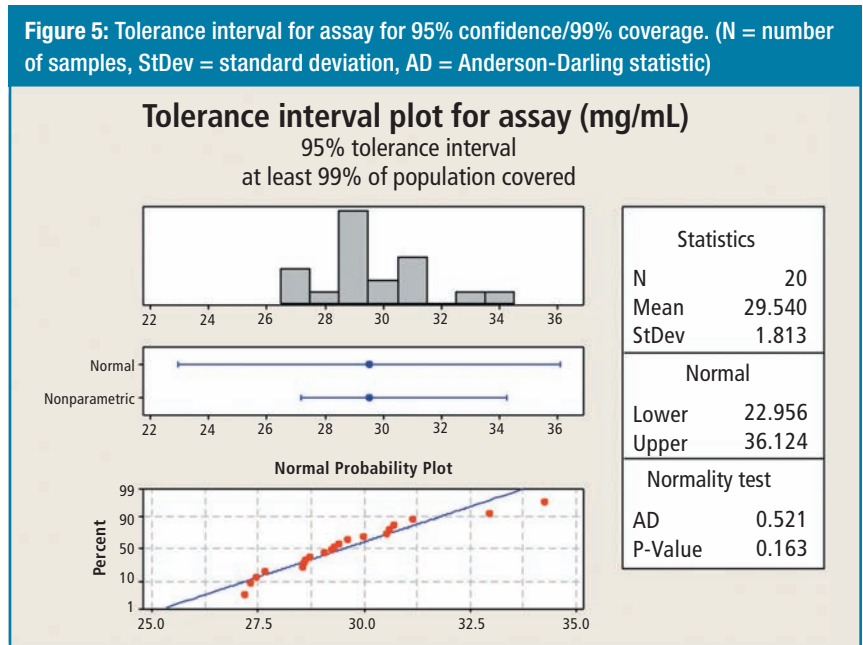
variance (ANOVA) confirms that the lot-to-lot variance component is not significant, which allows the data from the five lots to be combined to calculate a tolerance interval.

Statistical software (5) or tables from ISO standard 16269-6 (6) can be used to calculate the limits of the tolerance interval. **Figure 4** shows the calculation of the tolerance interval for the data set using a 95% confidence and the 95% coverage. Included is the Anderson-Darling normality test on the data set. Since the p-value is above 0.05, one can conclude that this data set is a good fit to a normal distribution and use the normal tolerance interval limits of 24.5 and 34.6 (results are rounded). It is important that the tolerance interval limits are within the specification limits of 20–40. If the tolerance interval limits were not, then there is a probability that the process would produce out-of-specification assay results.

Since PPQ lots should represent the same process population as the supporting Stage 1 data for assay, the PPQ lots' assay results will fall between 24.5 and 34.6 mg/mL for 95% of the time with 95% confidence. This acceptance criterion is tighter than the specification limit (20–40 mg/mL) and represents the observed process variation (both within and between lots) from Stage 1 studies.

To evaluate PPQ lots for within lot variation, one should select the sample size per lot with sufficient statistical power (e.g., 0.8 to 0.9) for the amount of variation they intend to detect. Detecting small variations within lots with sufficient statistical power may require a substantial sample size.

The same approach used to calculate the Stage 1 data tolerance interval can be used on the actual PPQ lot assay results post hoc. In this case, the acceptance criteria will “demonstrate with 95% confidence that at least 95% of the assay results are within the specification limits.” First, one must perform an ANOVA and confirm the between lot variance component is not significant in order to combine the data sets. When the PPQ lots tolerance interval



limits are calculated, they must be within the specification limits.

Multiple levels of tolerance intervals can be applied on a single CQA or one can use wider coverage and high confidence levels for CQAs that have a higher risk to patients. **Figure 5** shows a wider (99% coverage and 95% confidence) tolerance interval of 23.0 to 36.1 mg/mL (results are rounded). Assay results from PPQ lots should fall within this wider interval 99% of the time with 95% confidence.

Tolerance intervals are also useful when re-qualifying legacy products or setting action limits when implementing Stage 3, continued process verification. The tolerance interval for a CQA can be calculated from a series of historical lots. Newly manufactured lots should fall within the tolerance interval limits with the defined coverage and significance. If the CQA fall outside of the coverage limits, it may be indicative that the new process lots are not part of the same population of historical lots.

Conclusion

This article described the potential flaws of using end-product testing and in-process specification limits as the sole acceptance criteria for PPQ lots.

That approach indicates whether the PPQ lots have acceptable product quality, but does not predict if future lots will continue to do so. Because pharma companies are required to qualify the process as it was designed (in Stage 1) and demonstrate its reproducibility, they must establish additional acceptance criteria to demonstrate that the process is predictable for manufacturing future product. Statistical methodologies of prediction models, process capability, and statistical tolerance intervals can be used to develop more meaningful PPQ acceptance criteria and demonstrate that a designed process and its control strategy can reliably product quality product throughout its lifecycle.

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Evaluating Package Integrity

Hallie Forcinio

Industry awaits the final revision of *USP* General Chapter <1207> and the impact it will have on the evaluation of sterile product package integrity.

A proposed revision of the *United States Pharmacopeia (USP)* General Chapter <1207>, Sterile Product Package—Integrity Evaluation, calls for a shift to more quantitative, validated test methods. Although there is no set timetable, industry observers expect the chapter to be effective at the end of 2016.

“The first round of proposed revisions were included in the *Pharmaceutical Forum (PF)* in September 2014,” says Justine Young, project manager, container closure integrity testing (CCIT) at Whitehouse Laboratories. “The comment period has elapsed, and feedback has been received,” adds Brandon Zurawlow, who also serves as a project manager, CCIT at Whitehouse Laboratories. “The expert committee is now in the process of preparing a second revision to be released to *PF*. If sufficient comments are received, the chapter will need to undergo an additional revision process,” he explains.

According to Oliver Stauffer, chief operating officer at PTI—Packaging Technologies & Inspection, the revised chapter “clearly outlines the various container closure integrity (CCI) test methods fit for use in the

pharmaceutical industry. It identifies deterministic methods that are quantitative and definitive in measuring the integrity of a package. It also identifies probabilistic methods that use qualitative information or attribute results derived from human judgment. The document strongly advises use of deterministic methodology to assure CCI.”

“Many of the technologies included in the revisions have been available for decades,” notes Young. “Despite this,” she says, “industry has continued to rely on probabilistic test methods to evaluate the integrity of parenteral packages.” Once the chapter is effective, she predicts, “FDA will become more stringent in its review process of package integrity data.”

Zurawlow adds, “From discussions with others in industry, FDA is already beginning this shift, and companies are beginning to receive pushback when submitting data obtained by the dye ingress method.” Whitehouse Laboratories already employs deterministic leak-test technologies and currently relies on vacuum decay, mass extraction, helium mass spectrometry, high-voltage leak detection, and laser-based headspace analysis systems.

Stauffer explains, “*USP* <1207> does not necessarily change methods or technologies. It changes the way that organizations relate to those methods and the information they offer [and] ... encourages organizations to adopt test methods that provide the highest level of quality assurance. The chapter removes gray areas within CCI,

highlighting some methods that have industry-proven capability, and drives industry to deploy solutions that have a higher detection capability.”

Regardless of the CCIT methodology chosen, testing should be quantitative, repeatable, reliable, and validated for each product–package system. Ideally, any test also should be nondestructive to prevent waste and loss of costly product.

As a result, it seems inevitable there will be a shift from probabilistic testing such as dye ingress to more deterministic methodologies. However, Louis Brasten, supervisor, routine and functional analysis/filling services at West Pharmaceutical Services, notes, “Chapter <1207> has become more of a guideline. No ‘one test’ is the key to defining a client’s closure integrity. It is the right combination of testing that shows the complete picture over the lifecycle of the product.” West relies on state-of-the-art equipment and CCIT techniques to paint a complete picture of CCI for the lifecycle of its customer’s products (see **Figure 1**).

Whitehouse Laboratories provides CCI method development and validation services for client-specific product–package systems in a cGMP, FDA-regulated laboratory environment. “We will work with clients to understand their product–package systems and to determine the most applicable CCI technology to employ for integrity evaluation, offering our knowledge and years of experience to optimize the use of these technologies,” says Young.



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Figure 1: Helium leak testing is one way West Pharmaceutical Services checks container and closure integrity.



In addition to contract packaging services, West offers components to help ensure CCI. Ready-to-use Flip-Off PlusRU sterile drug-vial seals help to ensure injectable drugs are sterile and free of contaminants and particulates that could present risks to patients. “In recent years, changing regulatory guidelines have increased the demand for reliable seal solutions in the pharmaceutical industry,” said Mike Schafers, vice-president, global marketing, pharmaceutical packaging systems at West, in a news release. “Using high-quality sterile packaging components minimizes the risk of external contamination, line stoppages, and equipment down-time” (1).

According to West, Flip-Off PlusRU seals are manufactured using its TrueEdge manufacturing process to provide the smooth, even bottom edge needed for high-speed filling and capping. Assembled in a controlled (not classified) environment, seals are sterile and support clean crimping under Grade A air supply to exclude bioburden. A certified bioburden prior to sterilization allows cGMP-compliant sterilization validation, thus enabling clean crimping processes in accordance with the latest quality trends and regulations (1).

Equipment and test methods

Several technologies are used for CCIT. The traditional blue dye test submerges

the package in water mixed with blue dye. It’s a destructive test, and pass/fail decisions can be somewhat subjective because the operator is required to analyze the results.

Other CCIT options include camera-based machine-vision systems, headspace analysis (HSA), and leak detection. The latter can be based on vacuum decay, high voltage, or helium. HSA or one of the leak detection systems may be integrated with machine-vision systems or function as standalone units. These technologies are non-destructive, and some can be performed at line speeds to provide 100% inspection.

Christian Scherer, area sales manager, Seidenader Maschinenbau, discussed high-voltage leak detection (HVLD) and HSA in a presentation at the ISPE Manufacturing Solutions Conference at PACK EXPO East (Feb. 16–18, 2015) (2). Either technology can be integrated on Seidenader’s CS series camera-based inspection systems.

HVLD systems position the container between electrodes and detect changes in resistance. HVLD requires a non-conductive container and an electrically conductive liquid product. In addition, the inner surface must be wetted, and the distance between the electrodes and any defect must be relatively short. The container is rotated to scan the whole surface. Vials are held at the top and bottom with electrodes above and below, and syringes are positioned in a vertical orientation, needle down. In an integrated inspection system, containers feed into the vision system to identify visible flaws and are checked with HVLD on the outfeed to locate nonvisible cracks.

Often used for lyophilized product, HSA relies on tunable laser-diode absorption spectroscopy to detect oxygen content, water partial pressure, and absolute pressure in pharmaceutical containers. The laser is tuned over a defined wavelength range, and a photosensitive sensor measures the absorption profile of the headspace gas (3). If a leak is present, the resulting absorption line won’t match the reference reading.

At present, Scherer told the audience, use of HSA and HVLD technology is voluntary except in Russia, which requires machines to have integrated HVLD. “However, the investment in equipment versus the cost of a recall is minimal,” he concluded.

Vacuum-decay systems detect micro-leaks in empty and prefilled syringes, liquid-filled and lyophilized vials, and other liquid-filled packaging (both flexible and rigid). PTI’s VeriPac 455 vacuum-decay leak detector relies on core technology based on the ASTM vacuum-decay leak test method (F2338-09), which is recognized by FDA as a consensus standard for package integrity testing. The system’s patented PERMA-Vac dual-vacuum transducer technology increases test sensitivity and yields consistent, reliable results. The offline system is capable of detecting defects as small as 1.5 μm (4).

PTI also offers an offline laboratory instrument based on HVLD technology. The E-Scan 625 system detects pinholes, micro-cracks, and seal imperfections as small as 1 μm in prefilled syringes, liquid-filled vials, blow-fill-seal containers, and liquid-filled pouches. According to PTI, the HVLD method easily transitions from offline applications to 100% inline testing at high production speeds (5).

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Designing Trouble-Free Freeze-Drying Processes

Katriona Scoffin

Efficient freeze-drying processes result in time and energy savings, reduced failure rates, and improved batch consistency.

In a typical freeze-drying cycle, a product is placed in vials and dried on a shelf in a freeze dryer by first lowering the temperature sufficiently to ensure that the product is completely frozen. In the subsequent primary drying phase, the chamber pressure is reduced to induce sublimation of the frozen solvent (see **Figure 1**). A secondary drying phase is performed to achieve the required dryness.

The key characteristics of a freeze-drying cycle are the temperature and pressure gradients. The behavior of a product as it dries, however, is affected by many additional factors, such as vial size, condenser volume, product purity, batch size, and equipment specifications. The following aspects should be considered when designing a freeze-drying cycle and choosing freeze-drying equipment.

Optimize freezing conditions

There are three main factors to consider when optimizing the freezing stage of the cycle: the product must be fully frozen; the ice crystal structure should be open to aid sublimation; and complete freezing should be achieved at as high a temperature as possible to save time and energy. Annealing and controlled nucleation can help create optimal freezing conditions.

Annealing. Freeze dryers can be programmed to incorporate multiple ramp and hold functions to achieve the required frozen structure. Some programs use an annealing process, which is a technique of raising and lowering

the temperature over a range of a few degrees to control the freezing.

Controlled nucleation. Studies have shown that with uncontrolled nucleation, the drying time for the last vial to nucleate could be almost 20% longer than the first vial and 45% longer than a vial made to freeze close to its thermodynamic freezing point by controlled nucleation (1). Controlled nucleation techniques (e.g., ControlLyo by Praxair) make it possible to induce freezing at the maximum safe temperature for the product. For every 1°C increase in the nucleation temperature, primary drying time can be reduced by as much as 3-4%, and the overall time to freeze the product can be reduced (1).

Supercooling. Supercooling is a phenomenon in which the product is cooled below its freezing temperature without ice forming, resulting in unpredictable freezing behavior that may be several tens of degrees below the measured thermodynamic freezing temperature. Because ice crystals require a nucleating point in order to form, supercooling is likely to occur in ultra-filtered pharmaceutical formulations. Controlled nucleation is a useful method for controlling this behavior.

Choose the right vacuum pump

Most common laboratory pumps, such as single-stage pumps, diaphragm pumps and central vacuum systems, are powerful enough for freeze-drying applications. Most freeze dryers require a pump with an achievable vacuum of the order of <1 Mtorr, measured directly at the pump, according to pump manufacturer data. This vacuum will provide

close to 100% of the pumping-speed performance across the typical working range of freeze-drying vacuum requirements. If the freeze-drying system is specified correctly, then the condenser will trap all condensable vapors, and the pump will provide initial pulldown and maintain set vacuum. Vacuum-pump maintenance is often overlooked, but it is one of the more important day-to-day tasks that users can complete simply and easily to ensure the long-term performance of the freeze dryer.

Balance vacuum and temperature

The sublimation of ice crystals during the primary drying phase occurs due to the combination of vacuum pressure and temperature (see **Figure 1**). The system must achieve a vacuum lower than the vapor pressure of the frozen product temperature to begin the sublimation process. Getting the balance right is the key to achieving the fastest possible rates of sublimation. A common misconception about the drying phase is that the vacuum sucks the moisture out of the sample. If this were the case, then a lower pressure (i.e., a higher vacuum) could speed the process. In freeze drying, however, the purpose of the vacuum is to achieve sublimation of the frozen solvent. Increasing the vacuum further does not speed up this process; in fact, it actually slows it down, because fewer air molecules are available to provide heat to drive sublimation.

Consider condenser parameters

The temperature of the condenser isn't as important as trapping rate. To condense



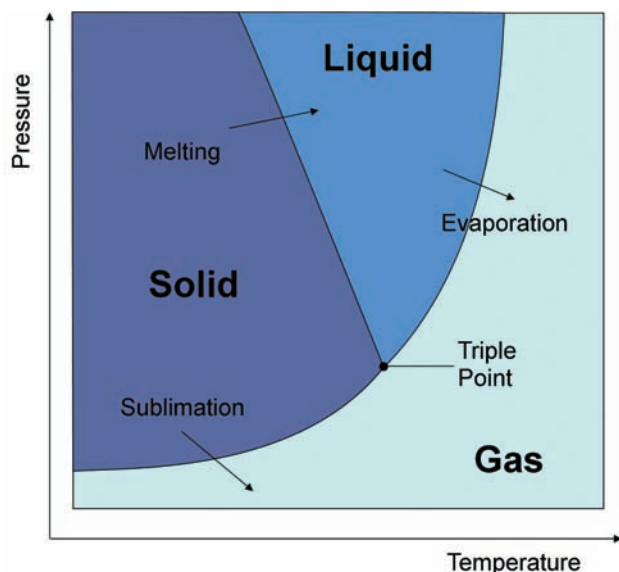
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PharmTech.com/Troubleshooting

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Figure 1: The phase diagram indicates how temperature and pressure changes can be varied to induce sublimation.



and freeze the solvent, the condenser needs only to be colder than the product in the chamber. Trapping rates are related to the design (i.e., size and shape) of the condenser. As the ice builds up, the temperature on the surface of the ice will not be as cold as on the condenser surface, and trapping rate might fall. If the deposition rate is exceeded, the risk is that vapor will bypass the condenser and potentially contaminate the vacuum pump, thus reducing its useful lifespan and increasing maintenance. A common misconception is that a colder condenser will improve freeze drying and ‘suck the water out faster,’ whereas specifying colder condensers for straightforward applications will simply increase the cost and complexity of the equipment. Colder condensers are best employed when processing solvents other than water that may have lower freezing points.

The actual rate at which drying can progress is far more influenced by the product itself and is highly dependent on the formulation’s parameters, the type of container (e.g., bulk trays or vials), and the fill depth per container. All of these data are used to calculate the total shelf area required to accommodate that load and the optimum choice of freeze-dryer design. On larger production dryers, it

is increasingly common to employ automated loading and unloading systems, and shelf spacing also needs to accommodate mechanisms of such equipment.

Choose the right container size

A cycle that has been prepared and adopted for a 10-mL vial with a particular fill depth will not necessarily be suitable for a differently sized vial, even with the same fill volume of the same product. Clearly, changing the vial size changes the product depth. This change may result in the product drying more quickly, therefore, requiring additional thermal energy from the shelf to counteract sublimation cooling, or more slowly, requiring less heat energy and extended primary drying. A small change in fill volume could also increase the overall vapor load of the batch, thus decreasing the drying rate or even overloading the condenser.

Different vial dimensions will affect the rate at which vapor can leave the product, which affects the speed of drying. This characteristic can be useful. For example, a cycle time can be decreased by choosing a larger vial with a shallower fill depth, but conversely the maximum number of vials per batch will also be reduced. It is important to find the right

balance between vial size, batch size, and cycle duration.

Tailor cycles to formulas

Different formulations of product will freeze dry differently. Concentration alone can significantly affect the processing characteristics of a product, which will consequently affect drying time and batch parameters. Different excipients have different thermal characteristics, so alterations to a formulation’s make-up can affect the freeze-drying cycle. Even small changes in formulation, batch parameters, and equipment can all have an impact on the process requirements. It is therefore not advisable to re-use an existing freeze-drying cycle for a reformulated product.

It is essential to know the critical freeze-drying parameters of a formulation, particularly when submitting for regulatory approval. Formulations for freeze drying often exhibit complex and unpredictable behavior, and detailed knowledge of this behavior is vital for effective cycle development. Significant thermal events include collapse, glass transitions, eutectic melting, and crystallizations. The most important critical temperature is the point below which the formulation must be cooled for complete solidification and maintained during primary drying to prevent processing defects. A variety of analytical techniques, including differential scanning calorimetry, differential thermal analysis, impedance analysis, and freeze-drying microscopy, can be used to identify freeze-drying parameters. It is advisable to use several analyses to ensure that a complete and accurate picture is formed.

When changing a formulation, for whatever reason, the product’s changing characteristics should be kept in mind. Not only will this prevent unexpected process failures later down the line, it may be possible to reformulate to provide a more favorable thermal profile and improve efficiency.

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SVETA DEMIDOFF/GETTY IMAGES

More Evidence that Size Matters

Jim Miller

Big service providers get bigger faster thanks to Big Pharma.

Size has proven to be a major competitive advantage in the clinical contract research organization (CRO) industry, and if that experience is any guide, it presages how the dose CMO industry will evolve as well.

The seven largest clinical CROs, six of which are public companies today, accounted for 52% of bio/pharmaceutical industry spending on CRO services in 2014, up from 45% in 2010 (Figure 1) (1). Over that period, the market for clinical CRO services grew almost 40%, to \$23 billion, but the top seven CROs collectively grew nearly 60%. They occupy an increasingly dominant position in a rapidly growing market.

The big CROs have extended their market share lead thanks in large part to their ability to secure preferred provider status with the 25 largest bio/pharmaceutical companies. Those global bio/pharma companies account for 60% of the industry's R&D spending, and an even larger share of spending on complex, expensive Phase 2B and Phase 3 clinical trials. Most large bio/pharma companies have embraced strategic relationships that involve transferring substantial portions of their clinical research operations to just two clinical CROs. These relation-

ships typically incorporate trial monitoring and data management activities, of which are both labor- and information technology-intensive; and may extend to other activities like medical writing and medical affairs.

The big CROs have extended their market share lead.

The global bio/pharma companies entrust the largest CROs with those critical operations primarily because of the CROs' relatively large size and scope of capabilities:

- They operate global networks that enable them to run multinational clinical trials with sites in dozens of countries
- They have the financial strength and infrastructure to absorb hundreds of staff transferred to their payrolls from the bio/pharmaceutical companies, and to take over a large number of ongoing studies in an orderly fashion.

Further, once they have secured these relationships, the large CROs have proven adept at maintaining them, using their operating skills to reduce the costs and time needed to execute complex clinical trials. In particular, they use their operating experience to ensure the trial protocols can be readily implemented; and they are making key investments in information technology to enable rapid data

collection and analysis and use that data for critical activities like site selection and patient recruitment.

The scale of these strategic relationships can be massive: Parexel generated more than \$300 million in 2014 from its relationship with Pfizer, and several other CROs receive nearly 50% of their billions in revenues from just five strategic clients. Such dependence on a few clients can be risky of course, but the tight integration with the client means that the switching costs for the client can be high.

Big pharma plays favorites

The preference for working with a small number of strategic suppliers appears to extend into the contract dose manufacturing market as well. Research by PharmSource indicates that while global bio/pharma companies seldom outsource the drug product manufacture for their new molecular entities (NMEs), when they do there are only a few select CMOs they appear willing to work with (2).

During the 2010–2014 period, global bio/pharma companies received 88 NME approvals, of which just 20 (22%) were outsourced to CMOs, including CMOs used as second sources of supply. Eighty percent of those outsourced NMEs went to only five CMOs. The same five CMOs also got the lion's share of opportunities for all global bio/pharma new drug application (NDA) approvals for which drug product manufacture was outsourced.

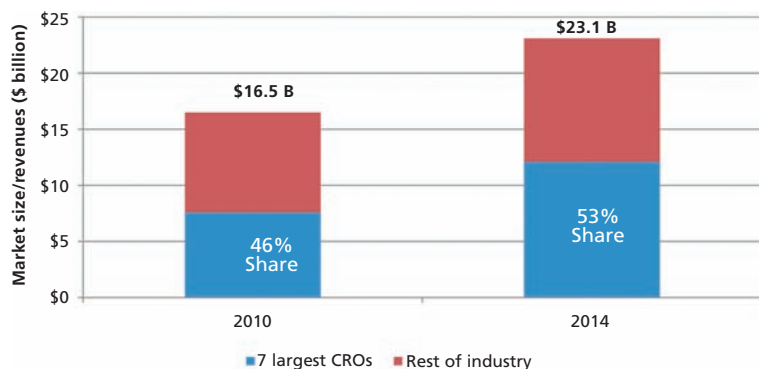
The concentration of CMOs serving global bio/pharma companies stands



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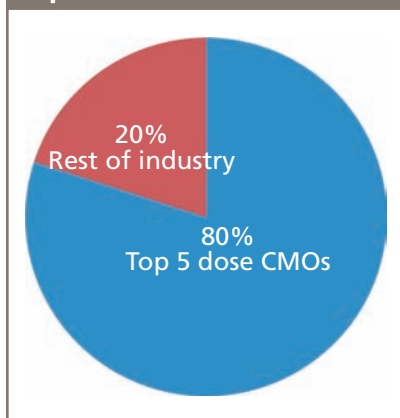
Outsourcing Outlook

Figure 1: Market share distribution in the clinical contract research organization industry.



Source: William Blair & Company, L.L.C.

Figure 2: Market share distribution of dose CMOs manufacturing global biopharma new molecular entities.



in contrast to the industry overall, as our analysis shows that at least 146 CMOs have benefitted from at least one NDA approval in the past 10 years. The *CMO Scorecard: Outsourcing of NDA Approvals and CMO Performance* shows, however, that the CMO industry is actually more consolidated than it may appear from the outside (see **Figure 2**).

Like their counterparts in the clinical CRO space, the five CMOs receiving the bulk of global biopharma NME manufacturing opportunities are among the largest in the industry in terms of revenues, are financially strong, and have good compliance records, so they represent secure sources of supply. Further, those companies

continue to invest in their capabilities and capacity to grow their business and gain even more market share.

The concentration of CMOs serving global bio/pharma companies stands in contrast to the industry overall.

Global bio/pharma companies have shown themselves willing to embrace strategic supplier relationships with service organizations that have the scale and scope to meet a broad range of their requirements. Only a few CMOs and CDMOs, however, have demonstrated the willingness to invest in the vision of a world-class development and manufacturing services provider. The evidence suggests that the opportunities may be out there if the industry is willing to step up to them.

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Practical Guidance for Successful Mammalian Cell Banking and Cell Line Characterization

EVENT OVERVIEW

Whether you're preparing GMP production or non-production master and working cell banks, end of production cell banks, or R&D cell banks, mastering the art of cell bank production requires specialized expertise, an optimal environment and instrumentation, appropriate quality controls, constant monitoring, close communication and continual troubleshooting. Further, the process for characterizing these cell lines can be extensive with an array of testing options available for specific scenarios. From adventitious agent testing to identity and genetic stability testing, it is important to know what options are available, when is the best time to perform these tests and how this will impact the overall project schedule and outcome.

KEY LEARNING OBJECTIVES

- How to plan a mammalian cell banking and cell line characterization project from start to finish.
- Practical tips for how to make a cell banking project successful, including best practices for cell banking suites, effective project management and how to work with a contract lab.
- Economical and time-saving tips for non-production bioassay cell banks.
- An overview of available testing for adventitious agents and various approaches.
- Recommendations for cell line identity testing and genetic stability testing.

WHO SHOULD ATTEND

Scientists, managers and directors in a Biopharmaceutical company who are responsible for cell line development and cell culture optimization or quality control.

Presented by



PRESENTERS

Jeri Ann Boose, Ph.D.
Sr. Director, Biopharmaceutical Services

Lana Mogilyanskiy, M.B.A.
Manager, Cell Banking

Heather Beyer, Ph.D.
Group Leader/Principal Scientist Viral Safety and Viral Clearance Services

Weihong Wang, Ph.D.
Technology Development Manager

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For questions, contact Kristen Moore
at kmoore@advanstar.com

While the technology is relatively new to pharmaceutical manufacturing, its potential is evident. The authors would welcome an active dialogue on how to accelerate the development of such capabilities across the spectrum of relevant processes.

Acknowledgements

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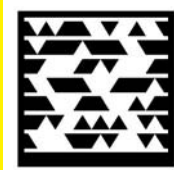


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FDA Issues Guidance on Environmental Assessments

FDA has issued a final guidance document for sponsors of investigational new drug (IND) applications and biologic license applications (BLA) recommending considerations for determining whether to submit an environmental assessment (EA) for gene therapies, vectored vaccines, and related viral or microbial products. The agency also details what information should be included in an EA.

The guidance includes EA considerations for INDs, BLAs, and BLA supplements for gene therapies and vectored vaccines for infectious disease indications. It also includes EA considerations for INDs, BLAs, and BLA supplements for related viruses and microbes that were generated using recombinant DNA technology. According to the guidance, "EA considerations for INDs, BLAs, and BLA supplements for live attenuated viral or microbial vaccines created by traditional methods, such as serial passaging and recombinant protein-based vaccines," are not addressed.

Kite Pharma Inks Deal to Spur Move into European T-Cell Market

On March 17, 2015, Kite Pharma announced that it would expand its T-cell capabilities with the acquisition of privately-held Dutch company, T-Cell Factory B.V. (TCF), which has now been renamed Kite Pharma EU. As part of the €20 million (approximately \$21 million USD) acquisition, TCF brings Kite Pharma TCR-GENERator, its proprietary technology platform that "rapidly and systematically

discovers, characterizes, and selects tumor-specific TCRs [T-cell receptors] of therapeutic value," according to a press release.

The acquisition also allows Kite Pharma to move further into the European market by providing access to European clinical manufacturing facilities. Earlier in 2015, Kite Pharma announced that it would further its T-cell platform with commercial manufacturing facility expansion in California. The addition of two facilities would support clinical trials, as well of the commercial launch and supply of KTE-C19. The lead investigational drug is an anti-CD19 CAR T-cell therapy in which the patients' T-cells are genetically modified to express a CAR that will target CD19 (a protein found on the cell surface of B cell lymphomas and leukemias), according to a press release detailing clinical results.

Valeant Adds \$1 Billion to Salix Offer, Amid Bid Battle

In February 2015, Valeant announced that it would acquire Salix for \$158 per share in cash, totaling approximately \$14.5 billion (including company debt). On March 16, 2015, Valeant announced that it would increase its offer to \$173 per share in cash coming to approximately \$15.8 billion, over one billion more than the original offer.

According to *The Wall Street Journal*, this increase comes after a cash-and-stock bid of \$172.56 from Endo International, a specialty pharmaceuticals company. Per the agreement, if all of the conditions to the tender have not been satisfied by Apr. 8, 2015, the offer price will revert back to \$158 per share, according to the press release.

Q&A with

David Barrett, chief operating officer at cut-e



Pharma has experienced many quality issues tied to manufacturing errors. Companies are spending millions of dollars each year to train, retrain, and assess their operators' and technicians' knowledge of cGMPs. The Behavioral Positioning System, developed by cut-e, a specialist in online testing, and online training developer GetReSkilled, aims to help life-sciences manufacturers see which behaviors and traits are most conducive to developing a quality culture and ensuring compliance.

PharmTech: Which individual personality traits and behavioral characteristics have you found to be more important to advancing a quality culture and regulatory compliance in the life sciences?

Barrett: We have found that the high performing pharma operators and technicians tend to be systematic, analytical, and focused on immediate tasks and results. They tend to be marked lower on traits such as wanting to act autonomously, setting overly demanding goals around achievement, or having very high levels of social confidence. This systematic behavior around quality and analyzing information, and focusing on tasks, suggests that these are good things to focus on in training and hiring for pharma.

At cut-e, we assess 14 million people a year in 31 countries across a number of different industries, not just pharma and life sciences, so it gives us some basis for comparison. The origins of our work in pharma come from years of experience in industries such as aeronautics, where safety is paramount, so we have a lot of research assessing airline pilots and engineers.

More recently, in our work with GetReSkilled, we've done research on life sciences, on models that seem to be indicators of safe behaviors, and the attributes that tend to separate people who operate well in life sciences from those who operate in an 'at risk' mode.

PharmTech: Tell us a bit more about the platform.

Barrett: The reporting and metrics can be used to target and identify training for manufacturing teams. With a less than optimum set of behavior metrics, BPS online video learning is used to strengthen positive behavior in the workforce.

It can also be used for high-volume screening of manufacturing personnel as they apply for jobs, or on making specific reports that aid selection, which you can pull and use when interviewing specific job candidates. Individuals, whether existing employees or job applicants, complete two short questionnaires. Results are then run through our benchmarks and algorithms and models based on large populations examining safe or unsafe behavior of workers in that industry. Using analytical tools in our system, one can determine whether or not an applicant is well matched to the job or whether an existing employee may need intervention to strengthen the necessary behavior for working in a GMP environment.



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