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2012 CONTRACT SERVICE OUTLOOK
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March 2012

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April 12-15, 2012 | Bethesda, Maryland | www.pda.org/lyoweek
- Fundamentals of Lyophilization | March 12-13
- Validation of Lyophilization | March 14-15

April 2012

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April 3-4, 2012 | Bethesda, Maryland | www.pda.org/visualsession2

The 2012 PDA Annual Meeting Course Series
April 19-20, 2012 | Phoenix, Arizona | www.pdaannualmeeting.org/courses
- Reprocessing of Biopharmaceutical Products – New Course | April 19
- Recommended Practices for Manual Aseptic Processes – New Course | April 19
- Biotechnology: Overview of Principles, Tools, Processes and Products | April 19-20
- Sterile Pharmaceutical Dosage Forms | April 19-20
- Implementation of Quality Risk Management for Commercial Pharmaceutical and Biotech Manufacturing Operations – New Course | April 19-20
- Process Validation and Verification: A Lifecycle Approach – New Course | April 19-20
- Process Simulation Testing for Aseptically Filled Products – New Course | April 20
- Investigating Microbial Data Deviations – New Course | April 20

May 2012

Environmental Mycology Identification Workshop
May 2-4, 2012 | Bethesda, Maryland | www.pda.org/mycology2012

2012 Aseptic Processing Training Program
Bethesda, Maryland | www.pda.org/2012aseptic
- Session 1: January 9-13 and February 6-10, 2012 – SOLD OUT
- Session 2: March 5-9 and March 26-30, 2012 – SOLD OUT
- Session 3: May 14-18 and June 4-8, 2012
- Session 4: August 20-24 and September 10-14, 2012
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Here’s to a Year of Compromise

It is in the New Year that we often set goals to improve ourselves, whether it’s trying to get fit, move up the career ladder, spend more time helping others in need, or any other number of personal quests. But individuals aren’t the only ones who make long-term goals—so do governments, organizations, and for our purposes, this industry. Harmonization of drug development and manufacturing approaches comes to mind.

I’m a big supporter and follower of harmonization initiatives, but I get the feeling that not everyone in industry is as gung-ho about the idea. At several industry meetings during the past year, I’ve asked people what they think of harmonization and whether they believe certain aspects of pharma manufacturing will ever be harmonized. I’ve asked conference participants, for example, about the necessity of each nation having its own pharmacopeial guide and of the existence of an international pharmacopeial guide. For biologic-license-applicants working to bring a product to the global market, is there a way to avoid filling out the same information on 20 different forms? Inspections are another area avoiding harmonization. We all know how many audit or inspection teams that companies must accommodate in a given year. Most of the answers I’ve received are along the lines of, “I don’t know,” “They would never agree to compromise on that,” or, “There’s too much national pride for one country to change its standards to match another’s.”

I get that compromise is difficult. In fact, I spent several years working for a nonprofit focused on the work of the United Nations, so I understand all too well how much effort is required to engage productive dialogue and garner compromise among a diverse and global audience. I also get that the biopharmaceutical industry is highly protective of its information and practices—it is a competitive, patent-based, trillion-dollar industry after all. But I also think that some of the key elements of harmonization are getting lost in translation.

Industry seems to want globally standardized approaches to their processes and quality systems as well as minimal routes for filing marketing applications and other required documents. Reaching these goals would make life easier for all parties involved. Having an agreed-upon, worldwide approach to quality and supply-management, for example, could literally solve many of the drug-product contamination and adulteration issues that have plagued the industry in recent years. And yet, many companies and national regulatory or standard-setting bodies seem unwilling to give up their current practices or accept that another company, organization, or nation for that matter, may have a better way of doing things.

Perhaps my vision of global harmonization is too lofty or naïve. But the reason to hope. The International Conference on Harmonization was established in 1990 with the aim of increasing “international harmonization of technical requirements to ensure that safe, effective, and high quality medicines are developed and registered in the most efficient and cost-effective manner.” In its 20-plus years, ICH has managed to gain consensus across North America, the European Union, and Japan, on 16 Efficacy guidelines, 10 Quality guidelines, 9 Safety guidelines, and has several multidisciplinary guidelines in the pipeline. The members of ICH’s Global Cooperation Group extend the reach of these guidelines to eight additional countries, including the leading markets in Asia.

Other global standard-setting bodies are working to shape global industry practice. And new industry groups working to share best practices throughout the world seem to be popping up every month. I hope you will take time to learn more about global harmonization efforts and talk with your colleagues about how your organization might become involved. In the meantime, BioPharm International will do its best to keep you apprised of happenings tied to harmonization and what it means for your day-to-day operations—and that’s just one of many resolutions we intend to keep this year. ◆
Stem Cells Create Diseases-in-a-Dish
Two recent articles highlight the utility of induced pluripotent stem cells (iPSCs) to create cellular models of disease that can be used to identify the mechanisms underlying disease-related pathology. In the first article, published online in *Nature* on Nov. 23, 2011, skin cells were collected from patients with a rare inherited neurodegenerative disorder called spinocerebellar ataxia type 3. The skin cells were used to create iPSCs that were, in turn, differentiated into neurons (1). The authors showed that calcium-dependent activation of the enzyme calpain resulted in insoluble aggregates of fragments of the protein ATXN3 in neurons derived from patients, but not from control individuals. They also demonstrated that the aggregates formed in neurons, but not in patient-derived fibroblasts or glial cells, suggesting a possible mechanism for the neuronal damage that occurs in patients.

In the second article, published in the December 2011 issue of *Nature Medicine*, researchers created iPSCs from fibroblasts collected from patients with Timothys Syndrome, a form of autism (2). The iPSCs were differentiated into neurons to examine potential abnormalities underlying the disorder. The researchers identified a host of abnormalities in the patient-derived neurons, including defects in calcium signaling, known to be associated with this syndrome, abnormal neurotransmitter production and defects in activity-dependent gene expression. Often, the genetic abnormality underlying a disease is known, but the details of how that abnormality translates into pathology are difficult to decipher. The ability to create cell culture-based models that reproduce the abnormalities found in human patients provides a powerful tool for understanding the mechanisms of disease.


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**Brazil’s Development Bank Leader Discusses the Country’s Pharma Future**

As part of the BRIC bloc with Russia, India, and China, Brazil is one of the world’s leading emerging economies and is also considered by IMS Health to be one of seven pharmerging nations, which also include Mexico, Turkey, and South Korea. With expectations to achieve significant pharmaceutical market gains in the coming years, *BioPharm* *International* spoke with Pedro Palmeira, head of the Pharmaceutical Department at the Brazilian Development Bank (BNDES) in Rio de Janeiro. The bank is the country’s primary financing agent for development.

**BioPharm:** It has been noted that Brazil’s northern region is growing at the same pace as most of China and that Brazil expects to continue to grow its economy. Are there key goals for the biopharmaceutical sector?

**Palmeira:** Brazil should continue growing at a rate of 5% per year in the next few years, largely driven by its internal market. In the case of the pharmaceutical market, the past few years have been prosperous, due to the increased income in the lowest levels of the population that began to acquire more health products, and to the increased public spending to attend the new public health needs of the population. This positive environment of the past 10 years has allowed for the modernization of the Brazilian pharmaceutical industry and its increased production capacity. The main challenge in the next few years will be to uphold the supply of health products for the increasing demand, while at the same time consolidating research, development, and innovation efforts within the country, especially in the area of biotechnology products.

**BioPharm:** The Brazilian government plans to move 16 million people out of poverty and into the healthcare system during the next 10 years. Is this part of a larger government initiative? What progress been made to date?

**Palmeira:** The recent economic boom in Brazil…, together with the government policies for income transfer, have taken more than 36 million Brazilians out of poverty, which increased the middle class by more than 50% of population. This result is extremely relevant for a country that still has a very high rate of income inequality. Even so, it is estimated that there are around 16 million Brazilians with a family income of less than US $45 per month, which are families that are difficult to reach by the traditional measures of the state. It was for these reasons that the Brazilian government created the Programa Brasil Sem Miséria (Brazil without Poverty) in 2011 to take this underprivileged group of Brazilians out of poverty and give them access to the country’s main social services. Within the scope of the program, healthcare is included as a fundamental right and an important pillar in the public policy to include this part of the population.

**BioPharm:** Moving so many people into the healthcare system will provide great business opportunity—as well as challenges—for the healthcare and drug sectors. What steps is the government taking to address these? What advantages may exist for biopharmaceutical companies outside of Brazil?

**Palmeira:** The key word to healthcare in Brazil is access. The government has been working hard to increase the supply of medicines to the populace. On the side of development and production in the country, this effort involves several fronts: technology transfer agreements via public-private partnerships; finance for the development and production of strategic products for the Brazilian health system; continued improvement of the regulatory regime; and centralized purveying and negotiating directly with producers. The opportunities for companies arise inasmuch as the government is able to acquire more products and sustain the adoption of new protocols in the Brazilian Universal Health System.
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BioPharm: What is the country’s short- and long-term perspective on the manufacture of biopharmaceuticals, including biosimilars?

Palmeria: The Brazilian government is working to construct an industrial platform for biotechnology within the country that, in the short-term, produces biological products that are not new (biosimilars). This industrial structure should, however, include the possibility to innovate and develop new biotechnology products in the long-term.

BioPharm: GE Healthcare and Amgen have recently made bold moves to acquire facilities and companies in São Paulo. Have you seen increased action along these lines from multinational biopharmaceutical firms? Do you expect more?

Palmeria: In the past two years, BNDES has received a growing number of consultations, both formal and prospective, from foreign companies in the health industry that are interested in the Brazilian market. Yes, we do expect more—and that these activities come to be real investments in the Brazilian health industry. Investments that contribute to the established industrial technology and that contribute to the challenge of increasing the access of the Brazilian public to health products and services will be very welcome.

BioPharm: Brazil’s regulatory system and healthcare policies seem to be stable and well-respected on a global scale, which have contributed to its role as a pharmerging nation. What components of this governance structure hold advantages for outside biopharmaceutical companies wanting to do business in Brazil?

Palmeria: Companies that wish to invest in the Brazilian health industry will encounter an extremely favorable environment.... Brazil has a regulatory regime and intellectual property environment that are in compliance with global standards, as well as a scientific and technological base that is consolidated and expanding. Finally, regarding long-term credit, BNDES and other government agencies offer favorable conditions to support industrial investments in production facilities as well in research, development, and innovation activities.

BioPharm: Brazil is known as a “pharmerging” market by the biopharmaceutical industries in North America and Europe. How do you view this label? How do you see your country in the global marketplace in terms of the biopharmaceutical space?

Palmeria: Today, Brazil is among the 10 largest economies in the world. With a population of 180 million, a vast territory and immense mineral wealth, the country is positioned as a promising economy. With a robust middle class, a diversified industrial base, a sustainable energy matrix, and a stable democracy that is anchored in solid institutions, the country is clearly on a path for growth—led not only by internal consumption, but also by a significant volume of exports. In this scenario, Brazil can legitimately aspire to be one of the world’s five foremost economies.

As far as the health industry is concerned, the scenario is even more promising as it is challenging. As mentioned, the income-transfer programs, together with economic growth, have brought 36 million Brazilian out of poverty to become real citizens able to consume goods and services. The improvements in quality of life of Brazilians have made Brazil, in just a few decades, a demographic pyramid similar to that of Europe. Life expectancy in Brazil is currently 73 years old. The change in the epidemiological profile of the populace is also impressive: today, the average Brazilian has more chronic-degenerative diseases than infecto-contagious illnesses. At the same time, it is important to point out the ambitious public health system which covers more than 100 million people. According to the Constitution of Brazil, health is the right of everyone and it is an obligation of the State to provide it.

Our pharmaceutical industry, which today holds the seventh rank in the world, grows by double digits, without indications of slowing down. Projections indicate that Brazil will occupy the sixth position by 2015. The Brazilian government has been stimulating the industry by supporting and financing projects that contribute to reducing the vulnerabilities of our health system—a fact that, together with a continually improving regulatory regime, has shown signs of the strategic nature of our health industry. Therefore, in this promising scenario, it is indeed possible to affirm that, more than having a label of ‘pharmerging market,’ Brazil has all the conditions to become a solid and developed pharmaceutical market in the short run, and it has huge opportunities for those that wish to take part.

BioPharm: The growing occurrence of South–South trade is leading to some multinational companies (as well as nations) to question their current market-growth strategies. How does your organization view South–South trade in terms of benefits, and perhaps disadvantages?

Palmeria: From our viewpoint, the increased volume of South–South trade reflects the search for opportunities and exchange among commercial partners with complementary interests. Specifically regarding Brazilian interest in developing a strong biotechnology industry in line with national interests, our country is obviously seeking partnerships with enterprises and governments where this technological wave has been consolidated, regardless of the regions or geographic location.

—Angie Drakulich
Election-year politics will play a role in a range of legislative and policy developments affecting drug development, manufacturing, and reimbursement in the coming year. Efforts to reduce government spending on healthcare are prompting all parties to search for opportunities to do more with less. Although FDA received a slight increase in its 2012 budget, limited resources throughout the public and private sectors are likely to undercut efforts to advance biomedical research and expand public health programs. These developments will drive manufacturers to look overseas for less costly and more efficient opportunities to expand R&D, production, and sales. As the campaign for the White House and control of Congress heats up, pharmaceutical and biotech companies will need to keep a sharp eye on how new policy proposals may affect product development, drug regulation, and the debate over reauthorization of the Prescription Drug User Fee Act (PDUFA).

**WHITHER REFORM?**

Manufacturers backed Obamacare two years ago as a way to expand the market for prescription drugs, including a growing number of pricey biotech therapies. In return, industry agreed to pay hefty new fees as well as higher rebates on Medicaid drugs, and to subsidize the cost of drugs sold to seniors caught in the “doughnut hole” of the Medicare prescription drug program. The worst-case scenario for manufacturers now would be to eliminate the market reforms and insurance exchanges designed to expand enrollment in health plans, while retaining provisions that cut revenues and raise costs for industry.

The 800-pound gorilla in the room is the looming Supreme Court decision on the constitutionality of the Obama healthcare reform legislation. While the Justices ponder the weighty legal issues, the US Department of Health and Human Services (HHS) will continue to implement the multitude of policies and programs established by that law. The administration’s working assumption is that the Affordable Care Act (ACA)—or much of it—will remain in place. Many states are moving ahead with efforts to expand health IT systems and to establish processes for determining insurance eligibility and coverage. But a Republican takeover of the White House in November 2012 would bring considerable changes in health-related programs.

Whatever the legal and political outcome, policymakers on all sides will be looking to cut payments to providers, to increase cost-sharing by patients, and to reduce benefits and services. Increased reliance on managed care plans and coordinated care programs, initiatives to reduce fraud and abuse, perennial proposals to reform the nation’s medical liability system, and efforts to curb pharmacy expenditures will emerge as ways to save money without compromising care.

**PRICING PRESSURES**

The drive for healthcare savings will continue to shine the spotlight on pharmaceutical pricing, reimbursement, and access. Policymakers increasingly will be looking for more convincing evidence of the value of new medicines and for new ways to reduce risk in determining coverage of new therapies. The Centers for Medicare and Medicaid Services (CMS), pharmacy benefits managers (PBMs), and other payers and insurers will ques-

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Rentschler Biotechnologie

Company Description
Rentschler Biotechnologie GmbH is a full-service contract manufacturer with over 35 years of experience in the development, production, and approval of biopharmaceuticals in compliance with international GMP standards with a highly skilled staff of 650. As part of the Rentschler Group and headquartered in Laupheim, Germany, Rentschler is one of three leading European CMOs operating globally. Dedicated to delivering high-quality biopharmaceuticals produced in mammalian cell culture, Rentschler has nine stand-alone GMP suites with 30-, 250-, 500-, 1,000-, and 2,500-L volumes, allowing material production for clinical trials and market supply. Rentschler Biotechnologie is a pioneer in the development and production of biopharmaceuticals—it was the first company in the world to gain market authorization for an interferon-containing drug.

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tion the value of high-cost therapies that appear to offer limited benefit. Payers and policymakers will face difficult questions about cost versus safety and efficacy, as seen in the debate over treatment of age-related macular degeneration with off-label use of the cancer drug Avastin (bevacizumab), instead of instead of its more costly formulation Lucentis (ranibizumab). Similarly, the controversy over the sharp price hike for preterm-birth treatment Makena (caproate) after it gained market control under FDA’s policy for halting sales of unapproved drugs, indicates that prices perceived as excessive can override some drug-safety issues.

Payers will continue to look for more drug discounts and rebates, threatening to relegate pricey products to unfavorable positions on health plan formularies. Although the Medicare Part D drug benefit has provided seniors with access to affordable medicines, benefits may suffer as many plans boost copays and limit coverage for costly therapies. In Europe, government agencies such as the United Kingdom’s National Institute for Health and Clinical Excellence (NICE) are opposing coverage of expensive products that lack sufficient added benefits.

Manufacturers are responding with risk-sharing programs that skew prices based on patient response to a new therapy. The claim by biopharmaceutical companies that effective treatment with expensive therapies can reduce overall healthcare costs will remain a hard-sell to the number-crunchers that regard pharmacy outlays as a discrete expenditure, rather than a way to save money.

Pressure to cut costs will drive support for the ACA provision that establishes a pathway for bringing biosimilars to market. FDA guidance on the scope of preclinical and clinical testing needed to document product comparability, if not interchangeability, will spur manufacturers of all stripes to move aggressively into the follow-on biologics field. For the program to be effective, policymakers will have to decide a number of thorny issues, including policies for names to identify these products, coding requirements for reimbursement, and rules governing patent challenges and protection.

Biosimilars are a big issue because payers anticipate hefty savings from these look-alike therapies, as has been the case with small molecules during the past 25 years. Generic drugs now account for about 80% of prescriptions in the US, and the proportion will rise further as more blockbuster brands such Pfizer’s Lipitor (atorvastatin) go off patent. The wave of new generic drugs puts more pressure on FDA to speed up its process for approving new generic drugs for market. New user fees paid by generic drugmakers will help fund such efforts.

Efforts by Pfizer to retain a good portion of the Lipitor market by cutting its price and negotiating long-term deals with payers and PBMs have roiled the drug industry and pharmacy programs. These actions further spur industry critics to harp about brand-generic patent settlements that can delay when a generic comes to market and propose policies to curb those practices.

**SECURING SUPPLIES; AVOIDING SHORTAGES**

The search by pharmaceutical companies for new products and new markets will further expand global pharmaceutical production, with the relevant opportunities and perils. Rising international sourcing of APIs and excipients will put more pressure on industry to manage production processes to ensure the quality and safety of their products.

A sharp rise in supply problems for vital drugs has led to a focus on drug quality and supply chain problems. The White House unveiled a drug-shortages initiative in October 2011, which supports proposals before Congress to broaden requirements for manufacturers to report to FDA production issues that could lead to supply problems. Policymakers also seek tighter controls on drug imports, better track-and-trace systems, and stiffer penalties for counterfeiting and drug adulteration. FDA officials are instructing pharma companies to police suppliers and distributors more effectively for early detection of quality problems. The regulators also want manufacturers to establish backup plans for dealing with supplier and production snafus that could halt production.

This increased focus on systems for ensuring reliable drug supplies will further intensify efforts by industry, FDA, and other regulatory bodies to promote continuous quality improvement strategies, including adoption of quality standards established by the International Conference on Harmonization (ICH). Regulators are looking to extend these quality assurance policies to include generic drugs and ingredients from other regions.

Efforts to manage manufacturing changes more efficiently will continue, as FDA officials promote more effective product testing and monitoring to reduce variability in drugs and biologics and to prevent “process drift” in manufacturing operations. FDA has proposed modified reporting requirements for certain postapproval manufacturing changes, with an eye to curbing unnecessary oversight. So far, however, manufacturers are disappointed by the limited scope of the regulatory changes.

Drug quality issues will keep up the pressure on FDA to conduct more frequent inspections of manufacturing facilities and to crack down on noncompliant firms, particularly foreign operators exporting products to the US. FDA is looking to expand partnerships and cooperative programs with regulatory counterparts in Europe and other regions as a way to combine inspection resources and
avoid redundant oversight. The regulators also are looking to tap into manufacturing data compiled by third parties to free up resources and focus on the most critical compliance issues. Agency officials hope to finalize a number of manufacturing and production policies in the coming year, but recognize that such efforts can be sidetracked by new crises and changing priorities.

Manufacturers who experience serious quality control problems face increased attention from federal and state prosecutors, who are looking more at violations of GMPs—in addition to off-label marketing and illegal pricing—as evidence of corporate malfeasance. Pharmaceutical companies have been hit with huge fines and onerous consent decrees for violation of GMPs and other regulations, but the situation may get worse. Government officials are raising the stakes by threatening to impose penalties on individual corporate executives who fail to take action to prevent such violations, and some of the saber-rattling could escalate into real blows.

**FILLING THE PIPELINE**

The loss of patent protection for a wave of blockbuster medicines is driving pharmaceutical companies to search for new models for drug development to fill an admittedly dry drug pipeline. Public and private backers of biomedical research talk more about “game-changing, transformational leaps” in discovery, as opposed to the incremental gains that traditionally lead to important scientific advances. There is growing enthusiasm for developing personalized medicines that provide more effective treatment based on individual genomic and metabolic characteristics. This will require the development of more diagnostics to identify key response factors.

Expanded international research efforts are tapping into public–private partnerships for developing important therapies for malaria, tuberculosis, and other diseases most prevalent in tropical climates. Health authorities are pressing for more research on new antibiotics, along with treatments for rare conditions and killer diseases such as cancer and AIDS. There is growing excitement about new vaccines, which are attracting more industry investment as markets mature around the world.

FDA can help the process, according to Commissioner Margaret Hamburg, who has been promoting the campaign to bolster FDA involvement in regulatory science initiatives to provide new tools and methods to accelerate the R&D process. Several programs are underway to validate biomarkers that can identify potential safety problems early on and improve the efficiency of clinical studies. Other coalitions are looking to streamline the long and costly R&D process by developing research protocols for “adaptive” clinical trials and promoting electronic methods for recruiting patients and collecting research data.

Yet, manufacturers complain that a risk-averse tendency at FDA and demands for more, larger studies keep many promising medicines off the market and raise R&D costs. The recent FDA decision to revoke the metastatic breast cancer indication for Avastin has generated questions about the future of FDA’s accelerated approval process and the threshold for bringing new cancer therapies to market.

FDA officials point to last year’s jump in approvals for new molecular entities (NMEs) as evidence that the agency is not keeping important new medicines from patients. A number of the approvals involve treatments for rare conditions and serious cancers that carry less risk for patients and lend themselves to speedy FDA evaluation.

The rise in overseas clinical research activity, as pharmaceutical companies seek more efficient drug development operations and data to support global marketing efforts, continues to focus attention on research ethics and policies to ensure compliance with good clinical practices. Several federal agencies are examining past unsafe research practices and weighing changes in policies and standards for clinical studies sponsored by the federal government or regulated by FDA.

Clinical research activities also face more scrutiny at home under transparency requirements that expand disclosure of active clinical trials and study results on the clinicaltrials.gov website. Health reform “sunshine” provisions require pharma companies to disclose payments to physicians and other health professionals, a process that involves major revisions in corporate policies and information systems. The transparency campaign, moreover, may result in broader FDA disclosure of information on drug safety and effectiveness, possibly even proprietary data that manufacturers might prefer to keep confidential. The assurance that US-supported investigators fully protect research participants and ensure the validity of clinical data is critical to improving public confidence in the pharmaceutical R&D process.

“Patient centeredness” will continue to shape regulatory and research initiatives. FDA is encouraging sponsors to incorporate patient needs and opinions into clinical-trial protocol design, patient recruitment, drug delivery, and safety evaluation. This approach will be supported by research sponsored by the Patient-Centered Outcomes Research Institute (PCORI), which is slated to have a $500 million annual budget by 2014 to study effective treatments for important conditions. PCORI plans to finalize priorities for its research agenda by March 2012, and its Methodologies Committee aims to report in May on research methods and standards for this field.
EMD Millipore

**Biomonitoring at EMD Millipore**

*We make the world a safer place*  

**A top player in the industrial microbiology market**

EMD Millipore BioMonitoring combines the experience and expertise of two historically strong players in the field of industrial microbiology and product process monitoring. The merger of EMD and Millipore in 2010 enabled this business field to become a leader in providing state-of-the-art testing methods, regulatory expertise and outstanding service.

**The acquisition of Biotest AG’s microbiology Business**

has recently been completed. It consists of the product portfolio of Hycon (hygiene monitoring) and the product portfolio of heipha Dr. Müller GmbH (microbiological culture media and microbiological test systems). It will complement EMD Millipore’s existing dehydrated cell culture media and testing systems with the so called “ready-to-use” culture media and instruments. It will also add particle counting and strengthen air monitoring in our hygiene monitoring portfolio.

This acquisition does not only allow us to strengthen our product portfolio in the growth segment industrial microbiology for contamination detection, it also allows us to capitalize on a motivated, customer focused workforce, unique knowledge and state-of-the-art production.

**BioMonitoring’s mission statement**

Across the globe, our microbiological Products and Services assure that food, water and pharmaceuticals are safe from biocontamination and our materials and components help to diagnose and treat patients worldwide.

**What supports our mission statement?**

We are a top-player in the Industrial Microbiology market.

- We have developed intimacy with regulatory requirements in the food & beverage, pharmaceutical and diagnostics markets
- We offer a comprehensive service and support for products, applications and process development
- We have a strong commitment and significant R&D investment towards innovation, with full understanding of customers’ evolving needs
- We have a decade-long track-record of standard setting leadership in core areas (Dehydrated Culture Media, Sterility testing, Blood-typing antibodies)
- Our customers can count on state-of-the-art production facilities. (ISO 9001-13485-14001; FDA–EMEA).

**Our market segments**

Focused markets include Pharmaceutical, BioPharma, Food, Beverage, Environmental (Municipal water), and Cosmetics.

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A new awareness campaign for BioMonitoring

“There is more to safety, than meets the eye” is the key message of the new awareness campaign recently launched to promote our offering in the growing microbiological monitoring market. This claim translates that safety goes beyond what is visible at first glance: the BioMonitoring offer goes beyond state of the art testing methods. We support microbiological monitoring through our expertise of local markets regulations and outstanding service. EMD Millipore provides that one invaluable result: maintaining the safety of your products and manufacturing processes.

**About EMD Millipore division**

EMD Millipore is the Life Science division of Merck KGaA, Darmstadt, Germany and offers a broad range of innovative, performance products, services and business relationships that enable our customers’ success in research, development and production of biotech and pharmaceutical drug therapies. Through dedicated collaboration on new scientific and engineering insights, and as one of the top three R&D investors in the Life Science Tools industry, EMD Millipore serves as a strategic partner to customers and helps advance the promise of life science. Headquartered in Billerica, Massachusetts, the division has around 10,000 employees, operations in 67 countries and 2010 revenues of $2.2 billion. EMD Millipore is known as Merck Millipore outside of the U.S. and Canada.

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www.emdmillipore.com/BioMonitoring  
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MERCK Millipore is the Life Science division of Merck KGaA, Darmstadt, Germany and offers a broad range of innovative, performance products, services and business relationships that enable our customers’ success in research, development and production of biotech and pharmaceutical drug therapies. Through dedicated collaboration on new scientific and engineering insights, and as one of the top three R&D investors in the Life Science Tools industry, MERCK Millipore serves as a strategic partner to customers and helps advance the promise of life science. Headquartered in Billerica, Massachusetts, the division has around 10,000 employees, operations in 67 countries and 2010 revenues of $2.2 billion. Merck Millipore operates as EMD Millipore in the U.S. and Canada.

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There is more to safety than meets the eye.
BioMonitoring by EMD Millipore.

BioMonitoring is about more than high quality microbiology testing solutions. It’s a comprehensive approach providing regulatory expertise, substantial service, and trust. These are vital components for the highly regulated pharmaceutical industry to produce that one invaluable result: safe products.

Our broader portfolio including Biotest Microbiology (heipha/Hycon) products:
- Microbiological membrane filtration
- Sterility testing
- Traditional and rapid microbial detection & identification
- Ready-to-use and dehydrated culture media
- Viable and non-viable air monitoring
- Surface monitoring
- Pyrogen testing

www.emdmillipore.com/biomonitoring

NOW: Including Biotest Microbiology Portfolio (heipha/Hycon)
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The year 2011 ended with the buyout of the contract research organization (CRO) Pharmaceutical Product Development (PPD) by two private-equity firms, the Carlyle Group and Hellman & Friedman. They paid $3.9 billion, a 30% premium over the company’s value shortly before the deal was announced, making it the largest private-equity deal for a publicly traded CRO.

Clinical CROs such as PPD have proven to be popular takeover targets for private-equity firms: PharmSource counts at least eight publicly owned CROs that have been taken private by private-equity firms since 2003 (see Table I). One CRO, PRA International, had a roundtrip. It was founded as a private company, taken public by its private-equity investor, Genstar Capital, in an initial public offering (IPO) in 2005, and then taken private again by Genstar in 2007.

MANAGEMENT INCENTIVES

Private-equity buyouts are usually quite attractive to the current shareholders of the company because they offer a significant premium over what the company’s stock was selling for shortly before the deal was announced. These deals are usually even more enticing to the senior executives who run the acquired company for two big reasons. Going private allows executives to pursue long-term growth strategies away from the oversight of public shareholders and Wall Street analysts, both of which may be more interested in short-term results than initiatives that promise longer-term, but more uncertain, payoffs. As importantly, the private-equity buyers usually offer the senior executives increased equity stakes in the company that can deliver great riches if those executives are successful in substantially increasing the value of the company through the successful implementation of those long-term strategies.

The PPD deal illustrates how senior management’s frustrations with the public market can drive a company’s board to pursue a private-equity buyout. In the past decade, the company had pursued a strategy it called “compound partnering” under which it would acquire or invest in promising early-stage drug candidates. PPD would undertake the early-development efforts to establish proof-of-concept, then out-license or sell the candidate to a drug company for late development and commercialization. Despite some early successes, the stock market and analysts following the company were uncomfortable with this strategy because it introduced a level of risk and uncertainty into a valuation model that expected steady financial performance that was easy to forecast. As a result of the uncertainty, the market discounted the value of the company’s stock. A similar problem had been a major reason for another CRO, Quintiles, to undertake a management-led buyout in 2003.

PPD’s board tried to improve its stock’s performance by making its compound-partnering

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business into a separate company, which it spun off to shareholders in 2010. That move, however, did not help the stock's valuation as much as had been hoped. Part of the problem had been the under-performance of PPD's laboratory services business, whose disappointing profitability in recent years has been blamed for depressing the company's stock price.

Private ownership may enable PPD management to address the laboratory businesses’ problems with a long-term view while shielding it from second-guessing by public investors. That was the story at PharmaNet Development, which was bought by a private-equity firm after it was cited for noncompliant behavior in running some of its clinical trials.

HOW PRIVATE EQUITY WINS

The aim of private-equity investors is simple: make a large cash return on the cash invested. This goal is accomplished in two ways: by taking advantage of the acquired company’s cash-generating capability and by making the company worth more when it is sold than when it was bought.

Most private-equity deals take advantage of the acquired company’s ability to support a significant debt burden. By using the target’s debt capacity, the private firm is able to borrow much of the purchase price and limit the amount of cash it must put up to make the acquisition in the first place. Current interest rates make borrowing especially attractive.

Clinical CROs are an attractive vehicle for leveraged buyouts. Their capital-investment requirements are usually small in comparison with manufacturing businesses, so they can throw off a lot of cash. Further, those cashflows are highly predictable because clinical CROs tend to have highly diversified multiyear project backlogs. A growing CRO is likely to be able to pay out substantial dividends to its owners as well as carry a substantial debt burden.

Enhancing the value of the acquired company may just be a matter of timing, such as by buying the company at a low point in the market cycle and going public when market multiples are high again. The private-equity firm also can improve the value of its target through further acquisitions, expansions of offerings, or restructuring to improve profits. Stock analysts who were following PPD before the acquisition speculated that PPD’s laboratory businesses might be in for restructuring.

RISKY PROPOSITIONS

Buyouts by private-equity companies are not without risk, as such moves are subject to not fully understanding the prospects of the business or changing market conditions. Both of these things appeared to happen to the buyers of the European CMO Nextpharma, whose Belgian injectables manufacturing business was recently forced to file for bankruptcy protection, as well as to the French CMO Osny Pharma, which filed for bankruptcy protection in early 2011 and was absorbed by another CMO, Cenexi.

While PPD’s track record of profitability and market position (it is thought to be the second largest for Phase I–IV clinical research after Quintiles) would seem to guarantee a strong performance over the typical private-equity holding period of five years, the changing CRO and bio/pharmaceutical research environment could present challenges. As global bio/pharmaceutical companies reduce their CRO relationships to a few preferred providers, competition for those relationships has become intense. There reportedly has been aggressive price cutting in the industry to get those deals, thereby leaving “winners” saddled with lower profit margins but losers shut out altogether.

Investors have been attracted to the CRO industry because the ongoing reinvention of the bio/pharma business model has outsourcing as a core strategy. The ultimate form of that business model is still evolving and being tested, and there is no guarantee that it will ultimately look like what it looks like today. Buyers of PPD bought one of the crown jewels of the industry. The greater risk is probably faced not by them, but the private-equity firms that bought PPD’s small and mid-size competitors.

Table I: Publicly traded contract research organizations acquired via private-equity deals.

<table>
<thead>
<tr>
<th>Company</th>
<th>Year acquired</th>
<th>Acquirer</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPD</td>
<td>2011</td>
<td>Carlyle Group; Hellman &amp; Friedman</td>
</tr>
<tr>
<td>Kendle</td>
<td>2011</td>
<td>INC Research *</td>
</tr>
<tr>
<td>Theorem Clinical (former Omnicare CRO)</td>
<td>2011</td>
<td>Nautic</td>
</tr>
<tr>
<td>inVentiv Clinical</td>
<td>2010</td>
<td>Thomas H. Lee Partners</td>
</tr>
<tr>
<td>Averion</td>
<td>2009</td>
<td>Comvest</td>
</tr>
<tr>
<td>PharmaNet Development</td>
<td>2009</td>
<td>JLL Partners</td>
</tr>
<tr>
<td>PRA International</td>
<td>2007</td>
<td>Genstar Capital</td>
</tr>
<tr>
<td>Quintiles</td>
<td>2003</td>
<td>Senior management</td>
</tr>
</tbody>
</table>

* CRO owned by private-equity firm Avista Capital Partners.
inVentiv was sold as part of a larger entity, Theorem was a unit of Omnicare.
Source: Company information and publicly available information.

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The biotech industry in 2011 scored victories with major drug approvals, deals, and advancements. But, while the industry was on pace for one of the biggest years of fundraising in the first half of the year, global economic worries and political fights over government debt in Europe and the US weighed heavily on financial markets and overshadowed the industry’s success.

These pressures not only hampered companies’ ability to raise capital in the second half of the year, but also raised the specter of cuts to governments’ expenditures on healthcare and biomedical research. With capital scarce and expensive, companies will need to focus their investments on clear paths to revenues. They will also have to develop products that push beyond incremental improvements, and concentrate on disruptive solutions that make healthcare costs more sustainable.

A total of 16 life-sciences companies managed to go public in the US through the end of November, 2011, raising a total of $1.4 billion, compared with 18 initial public offerings (IPOs) in the first 11 months of 2010 that raised a total of nearly $1.3 billion. As a group, the life sciences IPOs of 2011 fell 14.2% from their initial offering prices as of the end of November. Ten of these companies went public below their target prices and, as a group, these companies sold nearly 28% more shares than they set out to sell while raising about 14% fewer shares than they had hoped.

Therapeutics developer Endocyte, which went public at less than half its target price, was the biggest gainer through the end of November, closing up 71.3% to $10.30*. The medical-device company Kips Bay Medical was the steepest decliner, falling 80.1% to finish in November at $1.60. Public-market volatility weighed on public financings overall. US follow-ons fell 20.4% and private investment in public equity offerings dropped 33.1% from year-ago levels through the first 11 months of 2011.

The nearly $7 billion invested in the sector through venture capital reflected a 13.5% increase over last year through the first 11 months. But there are growing concerns about the future role of traditional venture investors who will play in funding biotech. Scale Venture Partners will exit the life sciences altogether, while the life-sciences practices at Morgenthaler and Advanced Technology Ventures are breaking off from their information technology counterparts to form a new firm. Meanwhile, Prospect Ventures said in October 2011 it would not raise a fourth healthcare fund and will return committed capital to limited partners.

In fact, a survey from the National Venture Capital Association has found that nearly 40% of life-sciences venture-capital firms plan to invest less in the sector during the next three years. That reduction reflects both frustration with regulatory barriers and the weak market for IPOs that have made it difficult for venture investors to cash out of their investments. These are troubling developments that could constrain the availability of capital to promising young companies in the years ahead. It is vital that regulatory barriers and capital market constraints be addressed that ultimately may be choking off important sources of innovative medicines and new jobs.

On the mergers and acquisitions front, 2011 saw a conclusion to the long negotiation between Sanofi and Genzyme. Divergent views on the value of the pioneering rare-disease biotech were closed with the use of contingent-value rights. Those rights could add as much to $3.8 billion to the agreed on $20.1 billion deal. Other notable deals included generic-drug giant Teva buying the biotech Cephalon for $13 billion; Japanese drug giant Takeda buying Switzerland’s Nycomed for $13.7 billion to broaden its access to Europe and emerging markets; and Gilead’s planned $11 billion pur-
chase of hepatitis C drug-developer Pharmasset*.

Through the end of November 2011, FDA approved 30 new drugs, more than the 21 it approved in 2010. Among the notable drugs that won approval were Vertex Pharmaceutical’s oral hepatitis C drug Incivek, Bristol-Myers Squibb’s melanoma drug Yervoy; the first new melanoma drug in 13 years and the first to extend the lives of patients with late-stage disease; and Human Genome Sciences’ Benlysta, the first new lupus drug in 50 years.

Personalized medicine also emerged as a bright spot for the sector with FDA’s approval of Roche’s melanoma drug Zelboraf and Pfizer’s non-small-cell lung cancer drug Xalkori. Both drugs were approved with companion diagnostics to determine which patients would benefit from their use. FDA also approved Seattle Genetics’ lymphoma drug Ad cetris, a drug that marries an antibody to a toxic chemotherapeutic payload to deliver a targeted therapy to a certain subgroup of lymphoma patients.

While the industry continues to raise a substantial amount of capital, much of it is going to fund large, well-established companies. The numbers don’t tell the full story. Smart companies will raise money when they can, rather than waiting until they need to raise money. Nevertheless, the pace of life-sciences IPOs is likely to accelerate in 2012.

Despite the increase in FDA approvals of new drugs in 2011, regulatory uncertainty continues to plague the industry. Increasingly we will see FDA move away from being a gold standard for the world to seeing it be a late adopter as companies move to win approval for innovative therapies in other countries first.

Though the US Supreme Court has said it will rule on the constitutionality of the Patient Protection and Affordable Care Act, the healthcare reform legislation passed in 2010 has already set in motion significant change. Regardless of the court’s ruling, meaningful reform will be driven by payers, physicians, patients and technology. The pace of that reform will only accelerate.

The end of 2011 also saw the expiration of Pfizer’s patent on its statin Lipitor, the best-selling drug of all time. In many ways the expiration of the patent marks an end to the blockbuster era of drugs. The future will be defined by targeted therapies informed by an understanding of a patient’s individual genetics. It’s a future in which we’ll be able to determine whether and for whom drugs such as Lipitor will provide any benefit. That is what patients and payers will both demand going forward.

* Burrill & Company is an investor in Endocyte and Pharmasset ♦
In the pharmaceutical industry, the most frequently audited facilities are without a doubt contract organizations. These organizations are constantly being audited by prospective clients, existing clients, global and domestic regulatory authorities, and their own staffs. They deal with due diligence, regulatory quality systems, routine GMP inspections, preapproval inspections, and internal audits on a monthly, if not weekly basis.

Audits can last anywhere from 1 day to 3 weeks depending on the type of audit being performed. In addition to typical audits, such as yearly GMP assessments by clients and regulatory authorities, contract organizations can also be tasked with “for-cause” audits by inspectors due to customer complaints or product recalls. Clients might also decide to perform a “for-cause” audit if the contract organization manufactured a number of lots with associated investigations for deviations during the manufacturing process.

To stay ahead of the audit game, contract organizations must have a system for handling audits that is efficient, consistent, and flexible. A great deal of experience among the audit team is necessary because the team must be audit ready all the time while also assuring that the company’s other departments maintain an audit-ready posture. The group must have the ability to host more than one audit at a time and be able to address questions and provide documents—in a timely manner—for as many as three auditors per group. The team must also be prepared to provide some of the same information to more than one group at the same time.

Admittedly, handling two separate audit groups with two to three auditors each is an unusual situation. However, let’s say that a contract organization has 14 clients and each client requires an annual GMP audit. To maximize audit time, each client brings two auditors and plans for a 3-day visit. Considering that each audit requires one day of preparation and one day of follow-up activities for the contract organization, each audit ultimately takes up one week of the organization’s time.

Let’s also assume that the contract organization is trying to attract new business. It has five potential new clients that wish to perform a quality audit before entering into a contractual agreement. In addition, let’s assume that the organization provides sterile injectable products (or a similar product) to the global market, placing it in the high-risk category of manufacturing. This classification would result in annual GMP audits from, at a minimum, the regulatory agencies of the US, Europe, and Japan. Agencies typically spend 1 to 2 weeks conducting cGMP audits.

Because contract organizations also must perform internal audits, which typically last one...
week and occur once a quarter, the numbers above equate to approximately 26 weeks or half of a year devoted to handling and conducting audits. This amount of time does not take into account preparation of responses to any potential audit observations or necessary follow-up activities.

To successfully accommodate all of these audits, a contract organization must maintain a full-time contingent. Organizations must be aware that the time commitment entails more than preparing and hosting audit groups. Each audit could easily take 4 to 5 weeks when considering preparation, hosting functions (both escorting and staging room activities), responses, and followup.

In addition, the organization must have a unique layer of resources to manage internal cGMP audit programs, which are required by regulators to ensure that each facility has a process for meeting compliance. Typically, these resources are passed on to customers as part of the cost for a contracted operation.

Given these expectations, there seems to be an opportunity for industry to work with consortiums such as Rx–360 or the International Pharmaceutical Excipients Auditing (IPEA) program to share audits and thereby ease overall costs and time tied to the audits. Moving in the direction of shared audits, however, requires more consistent interpretations and expectations, general acceptance of responses, and perhaps a certification process.

Companies using contract services must be willing to share their audit programs and compromise on what should be the ideal approach to assessing GMP compliance of contract organizations. They must agree to a set of criterion to be consistently applied for auditing and they must be somewhat consistent in their interpretation of the regulations. This would allow contract organizations to be able to maintain a robust quality system that is suitable for multiple clients. The use of shared audits has been discussed for quite a while and it seems that Rx–360 and IPEA have started down the road of solving the problem for raw-material suppliers. Let’s hope they agree to continue with the process and help out contract organizations in the same manner.

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Key speakers include:

- **Vasco Marcal Grilo,**
  Vice-President Global Pharma R&D Sourcing, **Johnson & Johnson**
- **Roger Gonourie,**
  Director Global Sourcing, **Novartis**
- **Nick Welby,**
  Procurement Director, **Astrazeneca**

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Throughout BioPharm International’s 25th anniversary year, we’ll be looking back at articles published in the first volume of the journal. This month, we rewind to “Separations Technology Outlook, Part II: Improved Recovery and Greater Purity.”

This article identified the major challenges with membrane technology as “considerable fouling from solids in the solution that clog the membrane, molecular weight and pore size specifications that often are inaccurate because of the inexact process of membrane fabrication, and vulnerability of membranes to degradation after repeated sanitization steps” (1). BioPharm International talked to Michiel E. Ultee, chief scientific officer at Laureate Biopharmaceutical Services and a member of Biopharm International’s Editorial Advisory Board, about what’s changed since the article’s publication.

**BioPharm:** Have the problems with membrane technology that the authors cited been resolved?

**Ultee:** Yes. Combination or layered membranes now incorporate prefilter layers to prevent clogging of the molecular-filter layers. Pore size, in terms of molecular weight, is still not precise, but most users have methods that take this into account by applying size-separation membranes only where significant size differences appear, such as concentration of proteins. Better materials are now available that resist degradation by sodium-hydroxide sanitization.

**BioPharm:** Have affinity membranes led to dramatic gains in purification efficiency and begun “to encroach on chromatography’s turf?”

**Ultee:** No. Affinity membranes have not really been accepted. The low capacity of membranes plus the high cost of affinity supports have prevented their acceptance.

**BioPharm:** During electrophoresis, can researchers now read gels in real time without staining them beforehand? Has electrophoresis become faster and more automated?

**Ultee:** Real-time staining is not yet possible with gels, but can be done with capillary electrophoresis, a technique that has evolved after a shaky start. Gel staining and destaining has become much faster and more sensitive.

**BioPharm:** Where will separation technology be in another 25 years?

**Ultee:** As the need for larger quantities of proteins emerges, processes will be developed that take advantage of technology available in the food and beverage industry. They will include techniques, such as precipitation, filtration, and resolubilization.

**REFERENCE**

Therapeutic Vaccine Outlook

Richard Whitworth

Therapeutic vaccines work on the premise that the immune system can be trained or optimized to take action against elements of a diseased state or condition already present in an individual. However, perhaps because of the immune system's complexity and incomplete knowledge of its pathways of action, only a few therapeutic vaccines have been approved to date.

Disease areas most commonly targeted by this immunotherapeutic approach are unsurprisingly those that have proven difficult to treat or cure through other means: AIDS, hepatitis B, and various autoimmune diseases are good examples. However, the use of therapeutic vaccines in oncological indications appears to have garnered the most interest. Researchers in this area found great promise in April 2010, when Dendreon's Provenge (Sipuleucel-T) became the first therapeutic cancer vaccine to be approved by FDA. Provenge is an autologous cellular immunotherapeutic for the treatment of asymptomatic or minimally symptomatic metastatic hormone refractory prostate cancer. Looking ahead, the market for cancer vaccines certainly has the potential for huge growth, with some reports indicating compound annual growth rates over 100% in the next few years (1).

Cancer Vaccines

Most cancer cells express tumor-associated antigens (TAAs) that can be recognized by the immune system as “foreign” and thus serve as potential targets for cancer vaccines. MART-1, MAGE-3, NY-ESO-1, prostate specific antigen, and prostatic acid phosphatase (PAP) are all examples of TAAs. Cancer vaccines seek to trigger a strong immune response to tumors by introducing TAAs into the patient possibly alongside adjuvants or immunostimulators and tend to fall into two camps. Tumor antigen-based vaccines can use peptides, recombinant proteins, tumor lysates, or killed tumor cells as TAAs. Cell-based vaccines, on the other hand, use ex vivo–prepared TAA-loaded antigen presenting cells (APCs) as the vaccine. In fact, it is the patient’s own APCs that are isolated from peripheral blood cells and loaded with TAAs in cell culture. Often, the precursor monocytes are cultured with cytokines to create dendritic cells (DCs), which are particularly potent APCs. Provenge is an example of this kind of cell-based vaccine; a recombinant antigen—a fusion protein consisting of PAP and the cytokine granulocyte-macrophage colony-stimulating factor (GM–CSF)—is cultured with the patient’s APCs in Dendreon’s manufacturing facility. Once the APCs have matured, they are infused back into the patient.

Looking at a few cancer vaccines in development pipeline, the picture looks quite bright, with tumor-antigen vaccines dominating over cell-based vaccines. Galena Biopharma’s NeuVax (E75) for breast cancer falls into the peptide-based category and has successfully completed a Phase II trial. The E75 peptide is derived from human epidermal growth factor receptor 2 (HER2) and also uses GM–CSF; together they stimulate cytotoxic T cells to target cells expressing any level of HER2. FDA has granted NeuVax a Special Protocol Assessment (SPA) for its Phase III Prevention of Recurrence in Early-Stage, Node-Positive Breast Cancer with Low to Intermediate HER2 Expression with NeuVax Treatment (PRESENT) study, which the company indicates will begin in the first half of 2012. Galena also announced in November 2011, the establishment of a clinical development collaboration with Genentech (a member of the Roche group) and The Henry M. Jackson Foundation for the Advancement of Military Medicine in which the two companies will sponsor a Phase II clinical study using NeuVax in combination with Genentech/Roche’s Herceptin (trastuzumab). Herceptin, a monoclonal antibody therapy, is currently available for patients with higher levels of HER2 expression.
Antigen Express, a subsidiary of Generex, has a similar product in development for breast cancer that is also a peptide fragment of the HER2 receptor called AE37. This is the company’s first candidate to take advantage of its li-Key Hybrid technology platform, which modifies fragments of antigens with the intention of increasing their potency in eliciting an immune response. Antigen Express is conducting a controlled, randomized, and single-blinded Phase II clinical study in HER2 expressing patients with either node positive or high-risk node-negative breast cancer. As with NeuVax, AE37 is administered with GM-CSF. The company released positive interim results for the study in August 2011. As HER2 is expressed in numerous cancer types, it has possibilities beyond breast cancer. Antigen Express has also completed a Phase I trial for prostate cancer.

Big Pharma is also trying to move forward with therapeutic vaccines. MAGE-A3 is currently in Phase III trials for the treatment of melanoma and non-small cell lung cancer (NSCLC) and forms part of GlaxoSmithKline’s antigen-specific cancer immunotherapeutic (ASCI) pipeline. The compound combines purified MAGE-A3 tumor antigen—a protein expressed in a large number of cancers in-licensed from the Ludwig Institute for Cancer Research—with a combination of immunostimulating compounds called AS15. The GSK ASCI pipeline also includes a treatment for acute myelogenous leukaemia at Phase II called WT1 and two other candidates at Phase I, NY-ESO-1 and PRAME.

Beyond vaccine development, GSK has also been working with Abbott Molecular on automated companion diagnostic tests for MAGE-A3 expression since 2009, and in November 2011, expanded the agreement to include the PRAME antigen. The polymerase chain reaction-based tests identify specific DNA sequences to help determine those patients most likely to benefit from the therapy.

Merck Serono is also in the NSCLC space with Stimuvax (BLP25 liposome vaccine), currently in Phase III, which it obtained with worldwide rights for development and commercialization from Oncothyreon. Stimuvax is designed to stimulate the immune system into targeting cells expressing glycoprotein MUC1, which is over-expressed or aberrantly expressed in many types of cancer. NovaRX is another company targeting NSCLC with its lead candidate Lucanix, which is also in Phase III trials that began in 2008. Unlike Stimuvax and MAGE-A3, however, Lucanix is a cell-based therapy that treats patients with four NSCLC cell lines that have been genetically modified to block transforming growth factor-beta. TGF-beta is produced by cancer cells and is thought to exert an immunosuppressive effect thus protecting them from an antitumor response.

A quick search of the National Cancer Institute’s clinical-trial database reveals a large number of potential cancer vaccines currently under development, more than a handful in Phase III. If they follow Provenge’s lead, the market growth predicted could become a reality.

**NICHE THERAPIES**

Although there is much R&D and, more recently, excitement in cancer vaccines, there are many other areas that could potentially benefit from therapeutic vaccines. ImmusanT (Cambridge, MA), for example, has zeroed in on celiac disease and is developing technology based on research performed at The Walter and Eliza Hall Institute of Medical Research in Melbourne, Australia, and at the University of Oxford, UK. NexVax2 is a combination of three short peptides from gluten protein that have been shown to cause an immune reaction in the 90% of sufferers with the HLA DQ2 gene, according to company information. NexVax2 is a peptide-based vaccine, but the aim, rather than increasing the immune response, is to desensitize its reaction to gluten. NexVax2 is progressing through to Phase II clinical trials.

The development of therapeutic vaccines as a new approach to combat substance abuse is another potential area for growth. Nicotine and cocaine are both examples of drug targets under development. The concept of long-lasting single injections, for example, removes the hurdle of the reliance on behavioral modification to control the intake of substances with the potential for addiction. Nicotine vaccines are designed to induce production of antibodies that bind to nicotine in the blood creating a molecule that is too large to cross the blood-brain barrier and thus cause pleasurable effect. However, Nabi Biopharmaceuticals announced on Nov. 7, 2011, results from its second Phase III trial for NicVax (Nicotine Conjugate Immunotherapeutic) and, unfortunately, preliminary assessment of the data showed that the primary endpoint was not met and there was no statistical difference between the NicVAX and placebo groups—these results are similar to the first Phase III study. Cytos Biotechnology and Novartis’ collaboration on NIC002, another compound designed to induce nicotine antibodies, also failed to demonstrate efficacy in Phase II trials after interim analysis.

Despite these failures, the market for antismoking products will no doubt continue to drive research into vaccines against nicotine addiction. As with other therapeutic vaccines under development, proving efficacy will remain a key challenge. 

**REFERENCE**

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The Conception and Production of Conjugate Vaccines Using Recombinant DNA Technology

Veronica Gambillara

In recent years, the vaccine market has experienced significant growth following the introduction of several novel bacterial vaccines—more specifically conjugate vaccines—addressing unmet medical needs. These conjugate vaccines are safe and effective against bacterial diseases and have been used in humans for many years. Although several serious bacterial infections, such as *Streptococcus pneumoniae* and some Meningococcal strains, are prevented using conjugate vaccines, the underlying process of development and manufacture has limited their scope. The method used for developing and manufacturing conjugate bacterial vaccines is based on chemical conjugation technology. It is a complex chemistry-based process that, depending on the pathogen or serotype, is time-consuming and expensive. A new approach has been developed to conceive and produce conjugate vaccines by employing recombinant DNA technology. This technology enables the development and manufacture of conjugate vaccines, called bioconjugates, and addresses the limitations of the current chemical conjugation process.

**BACTERIAL CONJUGATE VACCINES: AN IMPORTANT MARKET IN BACTERIAL INFECTIOUS DISEASE**

The vaccine market experienced significant growth over the past decade, with global revenues forecast to exceed USD $24 billion in 2010 (1). Within the growing market, conjugate vaccines for the prevention of bacterial infections today account for over 25% of the total market. In 2009, two of the four leading vaccines by sales were the bacterial conjugate vaccines Prevnar (Pfizer) for pneumococcal disease and Menactra (Sanofi Pasteur) for meningitis serogroups A, C, W-135, and Y. Together, these two products alone accounted for 12% of global vaccine sales.

Despite the success of glycoconjugate vaccines, several important bacterial infections lack a vaccine. These pathogens are responsible for significant morbidity, mortality, and cost to healthcare systems. Key pathogens that lack vaccines include *Staphylococcus aureus* and *Pseudomonas aeruginosa*, both causing nosocomial infections; *Neisseria meningitides* type B; and many diarrheal pathogens such as *Shigella* sp., enterotoxigenic *Escherichia coli* (ETEC), and *Salmonella* sp.

**THE LIMITATIONS OF CURRENT CONJUGATE VACCINE TECHNOLOGY**

The conjugate is a large glycoprotein molecule consisting of a protein linked or conjugated to a polysaccharide. The sugars are surface-exposed bacterial antigens to which the body will develop an immune response. The protein carrier is responsible for eliciting a long-lasting immune response against the polysaccharide, leading to better protection against the target disease, especially in young children (2). In chemical conjugation, the bacteria producing the polysaccharide and the protein carrier are grown separately, then purified through multiple steps. The polysaccharide is then chemically bound to the protein carrier (see Figure 1). This method faces the following challenges and limitations:
• Because the polysaccharide is produced by toxic bacteria, specialized and costly containment facilities are required. Moreover, several purification steps are necessary to obtain an acceptable purity of the product, thus resulting in loss of material throughout the process and decreased yields.

• Chemical coupling between the polysaccharide and the protein carrier results in a heterogeneous product which may still contain some free polysaccharide that may interfere with the immune response to the conjugates. Any small change in the mixture affects the characteristics of the vaccine, so the same mixture must be maintained throughout scale up and production—a manufacturing and regulatory challenge.

• Chemical conjugation can change the structure of both the polysaccharide and the carrier protein, thus making them less immunogenic, or in some cases, not immunogenic. Toxic polysaccharides must be chemically detoxified, often leading to further loss of immunogenicity or increased safety concerns.

The net result is that chemical conjugate vaccines are restricted to certain targets, may induce suboptimal efficacy, are difficult to develop, and are costly to produce. In addition, the growing resistance to antibiotics, the ever-increasing standard of safety, and high development costs required to bring a product to market emphasize the need for new technologies to address these challenges and fulfill the worldwide need for new vaccines.

NEW PROCESS FOR DEVELOPING AND MANUFACTURING CONJUGATE VACCINES

A new technology has been developed for the production of conjugate vaccines by an in vivo conjugation process. Instead of chemically conjugating polysaccharides to proteins, the conjugate is directly synthesized in appropriately engineered E. coli cells. Because E. coli is one of the fastest, least expensive, and highest product-to-volume systems available for the production of large molecules, the use of E. coli is appealing for the production of vaccines. However, until recently, it has not been possible to manufacture glycoprotein conjugates using bacterial cells.

Despite the ubiquitous presence of polysaccharides at the surface of bacterial cells, bacteria were thought to be unable to synthesize glycoproteins, and N-linked protein glycosylation was believed to be restricted to eukaryotes. The finding of N-linked glycoproteins in the human pathogen Campylobacter jejuni disproved this theory.

Various proteins of C. jejuni have been shown to be glycosylated by a heptasaccharide. This heptasaccharide is assembled on undecaprenyl pyrophosphate (UPP), the carrier lipid, at the cytoplasmic side of the inner membrane by the stepwise addition of nucleotide-activated monosaccharides catalyzed by specific glycosyltransferases. The lipid-linked oligosaccharide then flip-flops (i.e., diffuses transversely) into the periplasmic space by the flippase PglK. In the final step of N-linked protein glycosylation, the oligosaccharyltransferase PglB catalyzes the transfer of the oligosaccharide from the carrier lipid to Asn residues within the consensus sequence Asp/Glu-Xaa-Asn-Xaa-Ser/Thr, where Xaa can be any amino acid except Pro (3).

The gene cluster encoding this glycosylation machinery was functionally expressed in E. coli, allowing the heterologous production of Campylobacter glycoproteins in E. coli (4) and providing the first opportunity to produce N-linked glycoproteins in E. coli. In addition, the consensus amino acid sequence was introduced into different proteins that are not glycosylated in their original organism (see Figure 2).

The N-linked protein glycosylation biosynthetic pathway of Campylobacter has significant similarities to the polysaccharide biosynthesis pathway in bacteria (5). Because antigenic polysaccharides of bacteria and the oligosaccharides of Campylobacter are both synthesized on the carrier lipid, undecaprenyl pyrophosphate (UPP), the two pathways were combined in E. coli. The polysaccharide-syn-
Bioconjugation is versatile, enabling the attachment of virtually any polysaccharide to virtually any protein. This versatility permits the development of novel conjugates that cannot be addressed with existing chemistry-based processes.

- Bioconjugates are engineered to have a specific structure optimized for efficacy. Bioconjugate vaccines can be designed to not only generate an immune response to the polysaccharide, but also to the protein from the target organism, thereby enhancing efficacy. No free polysaccharide is present during bioconjugate production that can inhibit the immune response.
- Bioconjugates are produced in a standard, nontoxic bacterial production system, with no risk of contamination by mammalian infectious organisms. Moreover, bioconjugates are engineered to a reproducible structure and final product, thus minimizing potential safety concerns. This design will lower the regulatory barriers and potentially accelerate clinical development.
- Bioconjugate process development and production are rapid and straightforward. Producing vaccine by recombinant methods in a standard E. coli expression system and using a conserved biosynthetic pathway that may differ slightly depending on serotypes is a well-understood and commonly used manufacturing method.

From a technical perspective, the in vivo technology has the potential to provide uniform product, easily reproducible in a low-cost expression system, with an optimized safety and efficacy profile. These factors may decrease the regulatory barrier and the time to market and result in reduced development and manufacturing cost.

**CHALLENGES OF IN VIVO RECOMBINANT TECHNOLOGY**

The in vivo technology has the potential to overcome many issues that the chemical conjugation currently face in designing and producing conjugate vaccines. However, the following challenges are still unresolved.

- Because of the complexity of several bacterial pathogens, some vaccine candidates are still difficult to design and produce using in vivo recombinant technology. Bacterial pathogens such as N. meningitis B or Moraxella are challenging targets because the mechanism by which the antigenic sugar is assembled and expressed on the surface is less suitable for the in vivo glycoconjugation technology.
- The bioconjugate process is still early in development and its ultimate potential and limitations are not fully delineated. At this point, only data from preclinical and early clinical studies on a restricted number of pathogens are available. Additional work is required regarding process and assay development (i.e., scalability).

*Continued on page 32*
EVENT OVERVIEW:
Across the pharmaceutical industry, there is growing emphasis on the development of biopharmaceuticals as the next wave of therapeutic drugs and yet, there are many common analytical problems throughout the sector. Proteins, which must be analyzed using a variety of orthogonal techniques, including reversed-phase (RP), ion-exchange (IEX), and size-exclusion chromatography (SEC), present particular challenges for analytical chemists.

Bioseparations are difficult because large molecules carry so many functional groups. Charge is particularly important because it can form the basis of the analysis using ion exchange. Most often, ion-exchange separations are optimized by adjusting a gradient of increasing ionic strength, but it is generally recognized that the best selectivity is obtained by manipulating the charge of the molecule. Because the protein surface is covered with both weakly acidic and weakly basic functionalities, both the net charge and the three-dimensional charge distribution can be controlled with the buffer pH. Using this parameter to develop a separation can be tedious, requiring careful adjustment of pH of multiple buffers.

In this educational webinar, speakers will consider the challenges faced by biopharmaceutical laboratories today. We’ll discuss techniques to improve analytical methods for bioseparations by automating control of pH. Tools that can increase productivity and improve the robustness and reproducibility will be discussed, including how they can be used when paired with UPLC.

Researchers who will benefit from attending this webinar will include:
- Biochemists who need to perform HPLC and UPLC of biomolecules
- Biopharmaceutical laboratory managers who want to improve productivity and minimize errors
- Scientists looking to simplify protein separation method development and routine execution of methods
- Analysts who needs to test more intermediate separation parameters with accuracy and ease

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**PROOF-OF-CONCEPT STUDIES USING THE BIOCONJUGATE PLATFORM**

The process to create new and efficacious bioconjugate vaccines in a cost-effective and efficient manner has potential, but what is required is proof that such vaccines can be manufactured in commercial quantities, and that the vaccines produced are safe and effective. The following are examples that demonstrate the potential of in vivo bioconjugate technology:

A bioconjugate against *Shigella* sp. was produced under GMP conditions and tested for the first time in humans. *Shigella* is an important pathogen responsible for serious diarrhea and dysentery, so a vaccine to prevent infection in the emerging nations where it is present, as well as a vaccine for travelers, would provide a significant public health benefit. No vaccine exists for *Shigella*, despite ongoing research in many laboratories for several years. Attempts at vaccine development, both conjugate and live-attenuated bacteria, showed modest immunogenicity (8–11). Moreover, the technical hurdles to producing a conjugate vaccine with chemistry-based methods are very high. The bioconjugate produced against the serotype, *Shigella dysenteriae*, was tested in 40 healthy volunteers and found to be well tolerated. Importantly, the vaccine demonstrated a significant immunogenic response, and these immunogenicity data compare favorably to previous candidate vaccines tested against this pathogen. This promising Phase I data provide clinical proof-of-concept that the bioconjugate produced under GMP conditions by an recombinant DNA technology is safe and induces an immunogenic response in human.

The technology has been also applied for the development of a bioconjugate against *Staphylococcus aureus*. Nosocomial *S. aureus* infections represent up to 50% of all hospital infections. Moreover, methicillin-resistant *S. aureus* (MRSA) rates continue to increase dramatically. Despite significant research efforts undertaken by academic and pharmaceutical laboratories to develop a successful vaccine, there has been no recorded sustained effectiveness against *S. aureus* has been generated by the experimental vaccines tested (12, 13). More recently, the DNA recombinant in vivo technology was able to conjugate, for the first time, the main polysaccharides of *S. aureus* to a selected protein carrier of the same pathogen (i.e., antigen protein of *S. aureus*). This bioconjugate vaccine has been tested in animals and produced functional antibodies inducing protection in mice bacteremia and lethal pneumonia models (14). Although early, these results are promising considering recent clinical trial failures of *S. Aureus* candidate vaccines. The combination of polysaccharide and protein antigen against the pathogen will increase the immunogenicity of the vaccine at various stages and pathways of the infection, thus enhancing the possibility of protection.

These data demonstrate that this in vivo technology is a feasible approach for developing vaccines against challenging pathogens and offers the promise of improved efficiency in general.

**SUMMARY**

Antibacterial conjugate vaccines have become important tools for the public-health community to prevent serious bacterial infections. However, the complex development and manufacturing process has limited the potential of this important class of vaccine. This article describes a new in vivo process that incorporates a well-understood recombinant DNA technology in *E. coli* to manufacture bioconjugate vaccines. The process has demonstrated proof-of-concept in more than one bacterial pathogen, including a first-in-man study. Research is currently in progress to develop additional vaccine candidates and advance them into late-stage clinical trials.

**REFERENCES**

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Lyophilization or freeze drying is an important downstream process for stabilizing pharmaceutical compounds. The control and repeatability of lyophilization cycles are crucial for achieving consistently high product quality. Although the obvious parameters of shelf temperature and chamber pressure may be well controlled, the lack of control of the ice nucleation temperature (the temperature at which the product freezes) can adversely affect product uniformity and lead to suboptimal freeze-drying cycles. This study describes a novel means to control ice nucleation using a sterile cryogenic ice fog that is applicable to laboratory-, pilot-, and production-scale lyophilizers. Test results demonstrate the scalability and robustness of this technique.

Lyophilization or freeze drying is an important downstream process for stabilizing pharmaceutical compounds. It involves removing water and solvents from a product by sublimation and desorption to levels that will not support biological or chemical reaction. It is an excellent method to extend the shelf life of sensitive compounds for storage and transportation without subjecting them to detrimental high temperatures, and the only method available for a majority of biological compounds. Consequently, lyophilization continues to be indispensable to the pharmaceutical industry, despite its high cost and complexity.

Lyophilization consists of two major steps: freezing solutions, and drying the frozen solid under vacuum through sublimation and desorption. The drying step is divided into two phases: primary drying (i.e., ice sublimation) and secondary drying (i.e., liquid desorption). A successful lyophilization cycle can be defined by dried product that is visually and functionally acceptable with a short reconstitution time, potent active ingredients, and increased shelf life. The control and repeatability of the cycle are crucial for achieving consistently good product quality. Demand for lyophilization technology is growing because of the high value of the drugs being lyophilized as well as FDA initiatives such as quality by design (QbD) and process analytical technology (PAT). Consequently, the industry has been quick to develop and adopt technologies that facilitate improved control of key process parameters. Controlling ice nucleation during the freezing cycle of lyophilization is one such tactic that is currently under investigation as a means to achieve more robust and scalable lyophilization cycles.

The importance of ice nucleation temperature

The onset of freezing, or ice nucle-
Lyophilization

Lyophilization, is one of the most important steps in the lyophilization cycle. For nonaseptic systems a particle or impurity often serves as the nucleation point that allows ice crystals to grow and the product to freeze. However, in aseptic systems of high purity the product sometimes cools below its freezing temperature without ice crystal formation because no particulates are available for ice nucleation, a process known as supercooling. Substances that cool below the freezing temperature without becoming solid are referred to as supercooled. The degree of supercooling determines the ice crystal structure, which in turn characterizes product resistance to water vapor flow during the drying cycle. Increased supercooling has been shown to form smaller, more numerous ice crystals, thus resulting in higher product resistance and increased drying times. Studies have shown a 1–3% increase in primary drying time for every 1 °C decrease in ice nucleation temperature (1, 2). Supercooling of vials during freezing can thus increase cycle times and operating costs.

Lack of uniformity in ice nucleation temperature caused by vial supercooling can lead to vial-to-vial variability in ice crystal structure. Vials that freeze at high temperatures dry faster than those that freeze at low temperatures, making it difficult to have a drying cycle that is optimal for all vials. This variability causes problems such as vial breakage and melt-back, and decreases overall yield and product uniformity.

In addition, variability in ice nucleation increases the uncertainty in scaling up a cycle from laboratory (nonaseptic) to production scale (aseptic). A cycle optimized at lab scale may have entirely different drying time requirements at production scale due to the higher degree of supercooling expected in particulate-free, production-grade environments. Variability in ice nucleation is compounded by vial-to-vial variations in drying behavior due to variable ice structure.

Methods to address issues related to nonuniform ice nucleation

Although ice nucleation is an important parameter for achieving robust cycles, there have been very few attempts to achieve it at commercial scale until recently. The standard practice has been to use an annealing cycle, which involves raising the product temperature after freezing to a temperature above glass transition, and then holding. This method results in the formation of larger ice crystals at the expense of smaller ones, and helps minimize the variability in drying behavior. However, annealing may not be well tolerated by protein systems that are susceptible to denaturation. In addition, the benefits of shorter drying times may be offset by the additional time required for the annealing cycle. Lastly, annealing fails to address the root cause of variable ice structure, which is the lack of a uniform ice nucleation temperature, and can only help to repair the damage already caused.

Other methods that have been tried at laboratory scale include using nucleating agents such as silver iodide and bacteria, ultrasonic vibration of the product, etched

Figure 1: Illustration of a typical lyophilization system employing the scalable cryogenic ice-fog technique.

Figure 2: Illustration of the two-step approach for ice-fog introduction.

Shelves cooled at 0.5°C/min until desired nucleation temperature is attained

Cyrogenic Ice fog introduced for less than a minute

Viral nucleation detected (temperature probe + visual)

Water Vapor

Ejector

Liquid Nitrogen

ALL FIGURES ARE COURTESY OF THE AUTHORS
vials, sudden depressurization, and ice fog. This study will focus on the last method, ice fog, and show its successful transition from a laboratory concept to a commercially viable technique.

Ice fog as a means to induce uniform vial-to-vial ice nucleation

As discussed above, one approach for reducing supercooling and controlling ice-nucleation temperature is to introduce nucleating particles into the supercooled solution. A particularly advantageous nucleating particle is microscopic ice (i.e., frozen water) crystals in the form of a fog introduced into the freezing chamber (3). The concept of temperature-controlled ice nucleation was suggested by T.W. Rowe in 1990 (4). A cryogenically created fog containing microscopic ice crystals is introduced into the lyophilization chamber after the vials have reached the temperature at which nucleation is desired. The ice crystals subsequently make their way into the vials and induce nucleation inside the vial. Although this technique has found success on a laboratory scale, it has proven difficult to scale up to commercial lyophilizers. The difficulty is not only forming the ice fog and ensuring it is sterile, but also uniformly distributing the ice fog rapidly throughout the freezing chamber so that all vials are properly seeded with nucleating ice particles.

This article will describe a means to produce and distribute an aseptic ice fog that nucleates all vials in a short time. This work has resulted in a novel means to produce and distribute a sterile ice fog that is applicable to laboratory-, pilot-, and production-scale lyophilizers. This scalable cryogenic ice fog technology could provide a much-needed degree of control during lyophilization and thus facilitate application of QbD principles in this crucial downstream operation.

METHODS

Figure 1 is a schematic illustration of a typical lyophilization system employing the scalable cryogenic ice-fog technique. Creating a uniform dispersion of ice fog, distributing it into the freezing chamber and seeding vials with ice crystals for nucleation are achieved by a patent-pending technique involving contact between liquid nitrogen and water in a mixing device such as an ejector, outside the lyophilization chamber (see Figure 1). The ejector circuit is composed of a port for introducing ice fog into the freezing chamber and another port for recycling fog out of the chamber.

Ice-fog introduction followed the two-step approach shown in Figure 2. The vials containing the product to be freeze dried were placed on the cold plates inside the freezing chamber. In the initial phase of the freezing process, the vials were cooled to a suitable temperature at or below their freezing point. When the suitable vial temperature was achieved, a cryogenic ice fog was introduced into the chamber for about 30–50 s. Detection of ice nucleation in the vials was assessed by a combination of direct observation and temperature measurements on the outside of select vials. The metal door of the lyophilizer was replaced with a Plexiglas construction to facilitate visual observation and video recording.

In control experiments, the normal freezing cycle was run with no ice fog introduction. The goal was to determine the shelf temperature at which the first vials nucleate and freeze. This shelf temperature in subsequent
trials helped determine the trigger temperature ($T_g$) that indicated when the ice fog should be introduced into the chamber. The experiment also showed the extent of subcooling and vial-to-vial variability in freezing temperature by recording the range of temperature and time over which all vials nucleated.

Two sets of tests were performed using two lyophilizers. The first set was performed in a MINIFAST 1.0 (IMA Life) with 1.1 m$^2$ of shelf area and represented a laboratory-scale lyophilizer. The second set was performed in a LYOMAX 2.5 (IMA Life), with 2.5 m$^2$ of shelf area and represented a pilot or commercial-scale lyophilizer. Prefilled sterile vials were obtained for the testing, with between 10–20 vials arranged to be visible from the front of the chamber. Some vials were also strategically placed inside the lyophilizer on areas of the shelves where distribution of ice fog was expected to be most challenging. One of these vials was designated as the trigger vial (see Figure 3, Note 1). The temperature of this vial was monitored to determine when ice fog should be introduced into the chamber.

Of the total vials, nine were instrumented using K-type thermocouples. Vials without temperature probes were observed visually (see Figure 3, Note 4). All instrumented vials, with the exception of the trigger vial, had thermal probes mounted on the outside of the vials and touching the vial wall. The trigger vial contained the temperature probe inside the solution, but not touching the walls or bottom of the vial. Thus, it gave a truer indication of the solution temperature compared with the other instrumented vials where the temperature probe was mounted on the outside. However, it was also the vial most likely to freeze first because the probe itself served as a point of nucleation. $T_g$ was set at the temperature at which the trigger vial froze.

Two populations of vials were used in the same test. One population was filled with pure water only (see Figure 3, Note 2), and the other was filled with a solution comprising 5% glycine and 1% NaCl (see Figure 3, Note 3). All solutions were filter sterilized through standard 0.22-µm filters before use. A modular cleanroom was constructed around the front side of each lyophilizer to replicate the particulate-free condition of production-grade environments. A laser counter was used to measure the particle concentration inside the clean room, and it measured particulate (i.e., > 5 µm) impurity concentration to be under 15 particles/ft$^3$.

**RESULTS AND DISCUSSION**

**Creating and uniformly distributing cryogenic ice fog**

A key challenge for the commercial implementation of the ice-fog technique has been the creation of an ice fog that is sufficiently dense and that can be efficiently distributed to reach all vials in a large-scale lyophilizer. Because of this low density, not enough fog was available for all vials. Also absent in previous tests was an efficient system to distribute the ice fog within the freezing chamber and drive it into the vials. The system used in the present study produced a very dense fog and also distributed the fog throughout the freezing chamber within a short time (i.e., less than a minute). It is also possible, through this design, to control the density of the ice fog.

Fog creation and distribution were aided by the ejector assembly. The ejector serves two purposes. First, it provides an extremely efficient means for quickly forming the ice fog. Second, the suitably sized ejector provides enough pumping capacity to circulate the ice fog throughout the typical operation parameters of the lyophilizer.
freezing chamber rapidly. It is a significant advantage that the ejector can accomplish both of these functions without introducing any moving parts or other complicated mechanisms that would be difficult to steam or otherwise sterilize.

**Achieving ice nucleation in all vials at desired temperature**

Figures 3 and 4 show the temperature measurements obtained in control and ice fog experiments, respectively, as a function of time. Ice nucleation was indicated at the point when the temperature of a vial increased sharply. This result is due to release of the latent heat of fusion of the solution upon freezing.

For the control experiment, the first vial nucleated at a temperature of around $-9$ °C and the last vial nucleated at around $-18$ °C (see Figure 3). About 20 minutes separated these two occurrences, and the remainder of the vials nucleated at various times inbetween. This variation in ice nucleation time could increase in production-grade environments, where solutions may be supercooled further due to the absence of any particulates or impurities in the atmosphere.

Based on the data from control experiments, a trigger vial temperature of $-6$ °C was selected as $t_g$. The choice of this $t_g$ was conservative so that all vials were cooled below their freezing point. This choice was to ensure that absence of freezing was a result of supercooling only, and not because a vial was at a temperature above the freezing point. Sometimes uneven vial temperatures may occur in laboratory-scale lyophilizers because of nonuniform shelf cooling. In addition, the temperature probes, except the trigger vial probe, measured the outside vial temperatures which might not reflect the solution temperature inside the vial at all times. If all vials are cooled below their freezing point, ice fog can be introduced at a much higher temperature below 0 °C.

Shelves were allowed to cool at a ramp rate of 0.5 °C/min, and the temperature of the trigger vial was constantly monitored. When trigger vial temperature hit $-6$ °C, the ice fog was introduced. As seen in Figure 4, all vials nucleated at the same instant following the introduction of ice fog. Both vial populations, pure water and glycine solution, nucleated at about the same time on ice-fog introduction, indicating the general applicability of this technique for all supercooled solutions.

From a regulatory standpoint, creation of the ice fog at production scale does not introduce anything fundamentally new to the system. The ice fog is produced inside the ejector using steam and sterile-filtered nitrogen gas, both of which are already used in lyophilizers today (e.g., steam for sterilization and nitrogen for inerting or backfilling). All components downstream of the sterile nitrogen gas filter and up to the output of the ejector that releases the ice fog into the lyophilizing chamber have been designed to be sterilized in place. Hence, all the surfaces the ice fog touches before being introduced into the lyophilizer are sterile. All surfaces within the lyophilizer itself, including the vials, are sterilized, and the ice fog does not touch anything that is nonsterile, even

**Figure 4: Temperature measurements obtained in ice-fog experiments as a function of time.**

**Figure 5: Sequence of still frames from a 7-second video in increasing order of time from left to right. The first image shows the chamber before the introduction of the ice fog. The last image shows the chamber 7 seconds after the introduction of the ice fog.**
after being introduced into the freezing chamber. In summary, the introduction of a sterile ice fog is no different from the introduction of any inert gas, such as nitrogen, that is used today for backfilling vials. No additional sterility concerns should arise regarding the surfaces the ice fog touches inside the lyophilizer.

Introducing water in the form of ice crystals into a finished formulation may raise concerns initially. However, preliminary tests have shown that ice-fog derived water is a small fraction of the total water already present in the formulation, and comparable with the prevalent chamber moisture content that formulations routinely encounter when loaded into lyophilizers.

Ice nucleation in all vials was further confirmed visually and through video recording. Figure 5 depicts a 7-s video as a sequence of still frames separated by 0.4 s in real time. It shows the lyophilizer being filmed from outside the plexiglass door during the introduction of the ice fog. The first image in the sequence shows the chamber before the introduction of the ice fog, and the last image shows it 7 s after the introduction of the ice fog. The images clearly show a dense ice fog distributed throughout the chamber within this time.

Ice nucleation inside the vials can be visualized in Figure 6, which shows a 4-s video as a sequence of still frames separated by 0.3 s in real time. It shows the close-up of three consecutive vials placed in the center of the middle shelf of the lyophilizer, where ice fog reach is expected to be the most challenging. The first image shows the close-up of one vial just as it begins to nucleate after the introduction of the ice fog. Within 4 s, vials adjacent to it also nucleate and at the end of 4 s, all three vials have completely nucleated. On a macro scale, this phenomenon is seen in all vials inside the chamber, and all vials nucleate within 4–10 s following the introduction of ice fog. This result is a significant improvement over the 20-min vial-to-vial nucleation variability seen in the absence of ice fog.

**Scale-up considerations and potential regulatory concerns**

The scalability of the technique has been verified by replicating it on a lab-scale (MINIFAST) and a pilot-scale (LYOMAX) lyophilizer. It is expected to be easily scalable to larger sizes. The water-vapor source for ice-fog generation can be chosen based on ease of use and infrastructure availability. For instance, in nonindustrial, nonaseptic laboratories, a humidified gas stream may be the preferred source, whereas on the aseptic production floor, steam would be the preferred fluid.

**CONCLUSION**

Ice nucleation during vial freezing in lyophilization is an important process parameter that needs to be controlled. The scalable cryogenic ice-fog technology can be used in laboratory-, pilot-, and production-scale lyophilizers to induce uniform ice nucleation and eliminate vial-to-vial variability. Eliminating variability, in turn, can help mitigate a host of related issues and lead to improved process and product quality.

**REFERENCES**

Several scientific, quality control, and regulatory approaches are used to control and assess the risk of foreign substances that are inadvertently added to products that humans consume. The term extractables describes substances that might leach from a material’s surface into a solution while the term leachables describes substances that migrate from the material surface into the solution under the actual conditions of use.

In general, the following three possible negative effects result from the introduction of leachables into a pharmaceutical product stream.

• The leachable is toxic and poses a health risk to the consumer
• The leachable interacts with the drug product formulation so as to alter its stability and potency
• The leachable interferes with an assay that is crucial to measuring an important property of the drug product.

THE THRESHOLD OF TOXICOLOGICAL CONCERN

The threshold of toxicological concern (TTC) defines a generic exposure threshold value for groups of chemicals below which no appreciable risk to human health exists. The TTC approach is based on the analysis of the toxicological or structural data of a broad range of chemicals and was developed as a substitute for substance-specific information. The concept proposes that such a value can be identified for many chemicals, including those of unknown toxicity, when considering their chemical structures. Several excellent reviews have been recently published that summarize both the history and the scientific approach that TTC brings to risk assessment of chemicals (1–3).

In 1978, Cramer proposed that many chemicals, excluding polymers, could be categorized into three classes of compounds with three different potentials for toxicological risk (4). The categorization was based on a series of yes or no questions pertaining to structural-activity relationships (SARs), metabolic mechanisms, chemical reactivity, and other relevant information. Cramer class I substances have simple chemical structures and predictable and efficient modes of metabolism that suggest a low order of toxicity. Cramer class III substances permit no strong initial presumptions of safety, and may suggest significant toxicity, because their chemical structure has similarities to those of known toxins. Cramer class II substances cannot be placed in class I or class III and are therefore intermediate in expected toxicology. Cramer did not identify safe daily intakes for the Cramer classes but rather calculated a protection index that could be used to establish priorities and the extent of appropriate toxicity testing.

Table I presents a summary of the permitted daily exposures for the various classes of chemicals using the TTC approach.

The European Medicines Agency (EMA) has used the TTC approach to develop guidelines for genotoxic impurities (5). The Pharmaceutical Research
and Manufacturers of America (PhRMA) has also detailed a rationale for dealing with potentially genotoxic impurities in pharmaceuticals employing the TTC approach (6).

Perhaps the most notable use of TTC was in the 1996 report issued by the Pharmaceutical Quality Research Institute (PQRI) working group on leachables and extractables in orally inhaled and nasal drug products (OINDPs) (7). The PQRI working group concluded that the TTC level for carcinogens of 0.15 µg/person-day would be the safety threshold concern (STC) level for leachables in OINDPs. The qualification threshold for noncarcinogenic or nongenotoxic impurities was recommended to be 5 µg/person-day, rather than the 18 µg derived in the above table for food, based on an analysis of data of respiratory toxicities from three toxicological databases. The recommended threshold reflects the commonly observed trend that respiratory toxicities are generally greater than systemic, such as oral, toxicities.

There have been several compelling driving forces for approaching toxicological risk assessments from the TTC perspective. The first were regulatory requirements for public safety, such as the Delaney Clause. The Delaney Clause is a 1958 amendment to the Food, Drug, and Cosmetic Act of 1938 that states the following:

> The Secretary of the Food and Drug Administration shall not approve for use in food any chemical additive found to induce cancer in man, or, after tests, found to induce cancer in animals.

This requirement ultimately led to the Rawley proposal of the FDA Center for Food Safety and Applied Nutrition’s (CFSAN) Threshold of Regulation (TOR) approach. This approach determined the upper limit of concentration of a substance so that levels below that limit raised no concern that it might cause cancer at a statistically minimal (i.e., one in 10⁶) rate (8). Although proposed in 1986, a series of legal challenges prevented the codification of the TOR until 1995 (9).

The risk of inducing cancer in man or animals is not zero unless the impurity believed to induce cancer is also at zero concentration. The development of the TOR policy effectively resolves the issue that concentrations of impurities cannot be proven to be zero. Rather, impurity concentrations can only be shown to be less than the detection limit. According to data from the National Cancer Institute collected between 2002–2004, the lifetime risk of developing any form of cancer in the US is approximately one in three. Given this statistic, a risk of less than one in a million additional cancer cases for impurities below the TOR was as close to zero as the Delaney Clause could have intended. For example, an American’s current probability of getting cancer is 1 in 3, or 0.333333. Adding a 1 in 10⁶ additional risk would increase the probability of an individual getting cancer to 0.333334, clearly an immeasurable increase.

A second driving force for approaching toxicological risk assessments from the TTC perspective has been the increasing sensitivity of analytical methods used to detect and measure impurities, as well as ever more powerful techniques to obtain structural information on unknown compounds. While routine analytical methods in the 1950s measured most impurities in the fractions of percents, by the end of the century many analytical methods could often measure impurities in the parts-per-billion range, and much lower in certain cases. The commercial development of mass spectrometers (MS) of numerous types, but especially those attached as detectors to gas chromatography (GC–MS) and high-performance liquid chromatography (HPLC–MS) instruments, makes possible the identification, or partial or tentative identification, of many of these trace impurities. Once such trace-level impurities can be detected and identified, it becomes feasible to analyze the risk that they might pose. However, the effort and cost

<table>
<thead>
<tr>
<th>Table 1: Threshold of toxicological concern (TTC) summary. PDE is permitted daily exposure.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unknown compound type</td>
</tr>
<tr>
<td>Structural alerts for carcinogenic (but not in cohort of concern group)</td>
</tr>
<tr>
<td>Noncarcinogenic, possibly genotoxic</td>
</tr>
<tr>
<td>Nongenotoxic or carcinogenic grouped by structure-activity relationships (SAR) using modifications of the Cramer decision tree analysis</td>
</tr>
<tr>
<td>Organophosphate neurotoxin structure</td>
</tr>
<tr>
<td>Cramer class III (high complexity by SARs)</td>
</tr>
<tr>
<td>Cramer class II (moderate complexity by SARs)</td>
</tr>
<tr>
<td>Cramer class I (low complexity by SARs)</td>
</tr>
</tbody>
</table>
required to perform a risk assessment on one or two impurities are dramatically increased as the list of impurities for a risk assessment increases, even if the concentrations of the additionally detected impurities are extremely low.

The final driving force for approaching toxicological risk assessments from the TTC perspective has been recent concerns surrounding both the financial cost and ethics of animal testing (10). The European Union Registration, Evaluation, Authorization and restriction of Chemicals (REACH) program has been estimated to cost €1–2 billion (USD $1.56–3.13 billion) and would require more than a million animals if testing were done using current best practices (11).

Despite a large effort to further develop in vitro tests to minimize the number of in vivo animal tests, to date, only animal testing data can be reasonably extrapolated into humans. But a TTC approach to risk assessment may make some animal testing unnecessary. Some have proposed a combination of the TTC approach with intelligent testing strategies (ITS), which is premised on the idea that significant benefits will result from considering the methods used for hazard assessment in a holistic manner, rather than examining each method separately (12).

The most reliable data on human toxicological response are unquestionably from human epidemiology studies of historical chemical exposures, particularly when the dose can be reliably estimated. However, such data are only rarely available. Currently, animal testing is the next-most-reliable indicator of human toxicological response, and using SARs to predict toxicity, as is used in the total TTC approach, is currently the least reliable approach of the three. As more and more structures and toxicological information are entered into toxicology databases and as the algorithms using SARs improve, TTC will offer greater value. Furthermore, while in vitro and cell-based testing can be the “canary in the coal mine,” their ability to predict a safe human dose is currently extremely limited.

**Figure 1:** Strategies for minimizing the risks of leachables.
Table II: Safety guidance for drug containers from FDA Guidance for Industry: Container Closure Systems for Packaging Human Drugs and Biologics (17).

<table>
<thead>
<tr>
<th>Route of administration or dosage form</th>
<th>Safety guidance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inhalation aerosols, solutions, and nasal sprays</td>
<td>Case 1: Typically provided are US Pharmacopeia (USP) biological reactivity test data, extraction-toxicological evaluation, limits on extractables, and batch-to-batch monitoring of extractables.</td>
</tr>
<tr>
<td>Injections and injectable suspensions</td>
<td>Case 2: Typically provided are USP biological reactivity test data and possibly extraction–toxicological evaluation.</td>
</tr>
<tr>
<td>Sterile powders and powders for injection</td>
<td>Case 3: Typically, an appropriate reference to the indirect food additive regulations is sufficient for drug products with aqueous based solvents. Drug products with nonaqueous-based solvent systems or aqueous-based systems containing cosolvents generally require additional suitability information.</td>
</tr>
<tr>
<td>Ophthalmic solutions and suspensions</td>
<td>Case 4: Typically, an appropriate reference to the indirect food additive regulations is sufficient.</td>
</tr>
<tr>
<td>Topical delivery systems</td>
<td></td>
</tr>
<tr>
<td>Topical solutions and suspensions, and topical and lingual aerosols</td>
<td></td>
</tr>
<tr>
<td>Oral solutions and suspensions</td>
<td></td>
</tr>
<tr>
<td>Oral powders</td>
<td></td>
</tr>
<tr>
<td>Oral tablets and oral (i.e., hard and soft gelatin) capsules</td>
<td></td>
</tr>
<tr>
<td>Topical powders</td>
<td></td>
</tr>
</tbody>
</table>

**REGULATORY GUIDANCE IN PHARMACEUTICAL APPLICATIONS**

General guidance from FDA on impurities in pharmaceuticals can primarily be found in ICH guidelines Q3A, Q3B, and Q3C (13–15). The guidance in these documents focuses primarily on impurities caused by the synthesis of the drug, degradation of the drug, or residual solvents in the drug from the manufacturing process. These guidance documents do not directly address impurities from in-process leachables, but merely refer to “extraneous contamination that should not be present” that should be controlled by current good manufacturing practices (cGMP).

General guidance on equipment and materials used in manufacturing pharmaceutical can be found in 21 CFR 221.65 which states the following:

> **Equipment shall be constructed so that surfaces that contact components, in-process materials, or drug products shall not be reactive, additive, or absorptive so as to alter the safety, identity, strength, quality, or purity of the drug product beyond the official or other established requirements.** (16)

Perhaps the most specific FDA guidance in the area of leachables pertains to the final container closure (17). Focus on container closure is natural because the exposure time can be extensive—months to years—and there are no further purification steps to lessen any concerns about leachables. Table II is drawn from the FDA guidance for final container-closure systems and clearly delineates the importance of the route of administration of the drug.

The guidance on upstream, in-process leachables is appropriately less detailed because the risk is lower. A biopharmaceutical process extractables team recommended that the relative risk of various product-contact materials be evaluated with a risk–evaluation worksheet so that the highest priority will be given to materials known to potentially pose the highest risk. Among the variables in the worksheet are proximity to the API; extraction capability of the solution relative to the material and its potential extractables, time, temperature, and area or volume of contact; and cytotoxicity of extractables from the materials in tests such as USP <87> (18).

One of the common difficulties in the use of polymeric materials in a regulated environment such as pharmaceutical manufacturing is that the commercial lifetime of any polymeric material, or one of its components, is likely to be shorter than the commercial lifetime of a successful pharmaceutical drug. Most polymers are commodities subject to intense cost pressures over time, including newer manufacturing processes and lower-cost manufacturing sites. In the European Union, the Polymerforum Group was formed to foster better communication and strategies between polymer and pharmaceutical manufacturers around the issue (19).

The literature contains an illustrative example of a comprehensive analytical leachables study conducted after a film used as container closure was changed, although the risk-assessment portion of the study that presumably justified the change of materials was not included (20). The importance of change controls and supply-chain management when using commodity products such as plastics was recently emphasized (21). A comprehensive review of safety considerations related to leachables when using polymeric materials in pharmaceutical applications was recently published (22).
Table III: Toxicological risk assessment of leachables for three devices/applications. OINDP is orally inhaled and nasal drug product.

<table>
<thead>
<tr>
<th>Risk variable</th>
<th>Disposable bag (50-L bag)</th>
<th>Device and risk levels</th>
<th>OINDP in MDI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proximity to API(^1)</td>
<td>Low</td>
<td>Medium</td>
<td>High</td>
</tr>
<tr>
<td>Contact area/volume(^2)</td>
<td>Low</td>
<td>Medium</td>
<td>Medium</td>
</tr>
<tr>
<td>Contact time(^3)</td>
<td>Low</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>Contact temperature(^4)</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Difference of Hildebrand solubility parameter of extraction solution to material(^5)</td>
<td>Low</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>Material susceptibility to extraction(^6)</td>
<td>Medium</td>
<td>Medium</td>
<td>High</td>
</tr>
<tr>
<td>Subtotal concentration assessment(^7)</td>
<td>Low</td>
<td>Low–Medium</td>
<td>High</td>
</tr>
<tr>
<td>Exclusive use of 21 CFR cleared materials(^8)</td>
<td>Low</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>Cytotoxicity of leachables (USP &lt;87&gt;)(^9)</td>
<td>Low</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>Subtotal toxicology assessment</td>
<td>Low</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>Overall toxicological risk assessment</td>
<td>Very low</td>
<td>Low</td>
<td>Very high</td>
</tr>
</tbody>
</table>

\(^1\)High risk = final formulation; medium risk = downstream purification; low risk = upstream fermentation.
\(^2\)High risk > 1 cm\(^2\)/mL; medium risk = 0.1–1.0 cm\(^2\)/mL; low risk < 0.1 cm\(^2\)/mL.
\(^3\)High risk > 30 days; medium risk = 24 hours to 30 days; low risk < 24 hours.
\(^4\)High risk > 70 °C; medium risk = 37–70 °C; low risk = 2–36 °C.
\(^5\)High risk > 3 MPa; medium risk = 3 to X MPa; low risk < X MPa.
\(^6\)High risk = elastomers or plasticized polymers; medium risk are thermoplastic polymers; low risk are metals or glass.
\(^7\)TOC or NVR measurements from model streams can be used to estimate total concentration of leachables.
\(^8\)High risk = not 21 CFR cleared; medium risk = 21 CFR cleared but significant; low risk = 21 CFR cleared under comparable conditions of use application differences.
\(^9\)High risk = 100% cell death; medium risk = > 50% cell death; low risk = 0% cell death.

QUALITY BY DESIGN

In a quality-by-design (QbD) approach to manufacturing, the goal is to design in the quality of the final product by understanding all critical parameters and implementing robust manufacturing processes to control those parameters, as opposed to attempting to test in the quality from an unstable, poorly understood manufacturing process. The importance of QbD in extractables and leachables risk assessments, particularly in the OINDP application, was recently discussed (23).

In the risk assessment of leachables, the critical QbD goal is to understand and control the safety of the tool in the application. The author’s preferred process for achieving this safety is shown in Figure 1. The base of the pyramid is the responsibility of the tool manufacturer and is where most of the safety is built in, as indicated by its size. Knowledge of the technical literature could, for example, be used to understand and predict the impact of gamma sterilization on physical properties and the amount and type of gamma-induced leachables.

The green levels in the figure represent steps only the user of the tool can perform because they are highly application specific. The brown level represents steps that both the manufacturer and user of the tool can perform. The manufacturer of the tool tends to perform generic analytical testing, whereas the end user is more likely to perform analytical testing closely aligned with the application of the tool. The size of each level reflects the degree to which it helps lower the risk of leachables that affect safety. The key point in the graphic is to not be overly reliant on analytical chemistry and subsequent toxicological assessment of the analytical data, but to understand, robustly design in, and control the safety of leachables, rather than to test in the quality in the final application.

RISK ASSESSMENT

When Fawley published his milestone paper on the threshold approach to toxicology, the phrase “common sense” was prominent in the title (24). While it took many years to gain legal acceptance, the threshold strategy is now well entrenched and is being expanded on a global basis to a multilevel threshold strategy using the TTC approach. The FDA CFSAN still has only the single-level TOR, which individual scientists at FDA have described as too inflexible (25).

The pharmaceutical arena has seen some well-publi-
cized examples of leachables that potentially might affect patient health; virtually all were from container closures. Examples in the past few decades have included polycyclic aromatic hydrocarbons from carbon black fillers in elastomers, N-nitrosoamines or mercaptotriazoles in rubbers, and diethylhexylphthalates from plasticized polyvinyl chloride blood and intravenous bags and tubing (26, 27). Even permeation of leachables from labels and their adhesives through a low-density polyethylene film into a drug-containing vial has been observed (28).

In the biopharmaceutical industry, the published leachable examples are fewer due to the relatively short time that biologics have been manufactured. The issues in biopharmaceuticals seem more centered on API interactions with leachables and less about potential direct toxicological issues, undoubtedly due to the greater inherent instability of biologics relative to traditional small-molecule pharmaceuticals (29). Nevertheless, a rubber leachable after a formulation change apparently caused an increased risk of red-cell aplasia in European patients receiving EPO therapy (30).

Case histories of leachable problems present several clear trends in risks due to leachables. Because of their complex formulations and manufacturing processes, cured elastomers often have a much greater chance of having leachables with direct health risks than thermoplastics, and drug-leachable instability interactions are much more prevalent problems than direct leachable toxicity concerns. The higher risk of cured elastomer issues should be addressed by minimizing contact area and time, or selecting noncured (i.e., TPE) elastomers or over-molded elastomers (31). Drug-stability studies should be performed early in the material evaluation process, and analytical-leachables studies done to characterize the performance of acceptable materials or establish root cause for materials that reduce drug stability.

**THE KNOWLEDGE APPROACH IN RISK ASSESSMENT**

The goal of any risk assessment should be to promote a rational resource allocation to address potential problems, with the highest risk areas receiving the highest scrutiny. To assess the toxicological risk of leachables from product-contact surfaces, one must understand material science, solubility parameters, the effects of sterilization procedures such as gamma irradiation, application-specific parameters (i.e., contact time, temperature, surface area and volume, solution properties, and proximity to the final formulation), and relevant toxicology to assess the value of extractables and leachables testing.

This scientific assessment must be combined with information from the material supplier. Supplier information should substantiate that the raw materials have appropriate 21 CFR clearance for the application, the proper controls are in place for cGMP manufacturing, and whether available generic extractables or leachables data can help in the risk assessment. Often the risk assessment using the combination of the manufacturer’s generic leachables data with the end-use applicationspecific parameters and a TTC approach will conclude that further leachables studies are not necessary to establish the safety of the leachables in terms of direct toxicity.

Table III shows the analysis of the toxicology risk using a series of potentially important variables when using three devices in three applications, roughly based on the protocol suggested by the Biopharmaceutical Process Extractables Core Team (17). Other possible risks from leachables, such as product formulation instability or assay interferences, would be assessed separately.

The first section of the table contains estimations of six variables that could affect the concentration of observed leachables. The second section contains estimations of two variables related to the potential toxicological risk of the leachables. Rather than assign numerical values to each risk level, such as the 1–10 scale previously suggested, the overall risk is estimated with high, medium, or low categories. Rather than sum up the numerical risk levels to achieve an overall risk assessment, the relative risk of toxicology of the leachables and the relative risk of the amount of leachables are evaluated separately. The two risks are viewed as multiplicative, in line with the normal definition of risk as equal to the degree of the hazard times the level of the exposure. This separate evaluation allows for the possibility that if the toxicology is estimated to be low risk, then the concentrations of the leachable are not as important, much as in the TTC approach.

**SUMMARY**

As scientific progress continues to be made, methodologies are advanced, sources are better controlled, materials improve, and processes are upgraded and better measured and controlled, the best practice to assess the risk of leachables will further evolve. Science and understanding are not static. However, the fundamental understanding of all the technical issues...
regarding leachables and toxicological safety will continue to be applied to achieve a knowledge-based risk assessment.

REFERENCES

New Technology Showcase

**Needle-Stick Protection**

Catalent has partnered with Innovate UK to offer cost-effective and easy-to-use solutions for needle-stick injury protection through two device options. The Click In Safety Shield System provides a high-quality, cost-effective choice for needle-stick protection that can be used with all needle formats, including staked-needle, luer-lock, or luer-slip syringes in glass or plastic. The Protector Safety shield system offers an additional option for needle protection for use with luer-lock syringes.


**Depth Filtration System**

The Zeta Plus Encapsulated System is a single-use depth filtration system designed for the bioprocessing industry where upstream cell-culture clarification or downstream impurity removal is required. It features an ergonomically designed large holder that can be pivoted between horizontal and vertical position to allow convenient handling, minimal footprint, and minimal fluid spills.


**Process-Chromatography Equipment**

The Process Chromatography Station 00 includes Process Skid 00, a compact skid designed for automated, small-scale GMP biopharmaceutical manufacturing. Its process chromatography column and PrepStation unit enable media transfer and column lifting. Process engineers can simplify column preparation by selecting preprogrammed or manual methods for the process chromatography column and Process Skid 00.


**Protein A Media**

Novasep’s AbSolute High Cap is a modified silica-based protein A media for capturing monoclonal and polyclonal antibodies from high-titer and large-volume fermentation feedstock. The media has dynamic binding capacities, measured at 10% breakthrough, of 65, 55, 35, and 30 mg/mL at 250, 500, 1000, and 1500 cm/h, respectively.

*Novasep*, tel. +33 3 83 49 71 47, www.novasep.com

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PDA’s Training and Research Institute provides intensive, job-focused training that clients can apply immediately. The curriculum is designed to foster professional development in areas such as aseptic processing, biotechnology, environmental monitoring, filtration, microbiology, quality, regulatory affairs, training, and validation. Courses can be customized and provided at the client’s location.


**Aseptic Disconnector**

The Clipster aseptic disconnector is a single-use device for disconnecting silicone tubing. It is used after a fluid transfer to disconnect single-use transfer lines and bag assemblies in nonclassified or classified environments while maintaining product sterility in biopharmaceutical applications.

*Sartorius Stedim Biotech*, tel. 800.368.7178, www.sartorius-stedim.com

**Bioreactor Adapter Kits**

New Brunswick Scientific’s adapter kits enable 5- and 14-L CelliGen BLU single-use vessels to be used with a range of existing bioreactor systems, thus saving time and labor, as well as reducing validation and utility requirements. All vessel components in product contact are made of US Pharmacopeia Class VI materials and have been tested for extractables and leachables, making them appropriate for GMP environments.


**Contract Analytical Services**

SGS Life Science Services offers analytical chemistry, microbiology, stability studies, method development, protein analysis, and bioanalytical testing. With the acquisition of M-Scan’s laboratories, SGS’s portfolio now includes the characterization of biologics with GLP–GMP contract analytical services, consulting, and training based on mass spectrometry and chromatography.

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Patheon is a global provider of contract development and manufacturing services to the pharmaceutical industry. The company delivers products and services to approximately 300 of the world’s leading pharmaceutical and biotechnology companies. Patheon’s services range from preclinical development through commercial manufacturing of dosage forms, including parenteral, solid, semisolid, and liquid forms. Patheon’s technologies include single-use disposables, liquid-filled hard capsules, and various modified-release technologies.

Patheon’s range of fully integrated pharmaceutical development services includes preformulation, formulation, analytical development, clinical manufacturing, scale-up, and commercialization. Patheon takes customers’ products direct to the clinic with global clinical packaging and distribution services. Patheon’s Quick to Clinic programs can accelerate early-phase development projects to clinical trials while minimizing the consumption of APIs. Patheon’s integrated development and manufacturing network of 10 facilities, eight development centers, and one clinical-trial packaging facility across North America and Europe enables customer products to be launched anywhere in the world. Patheon, tel. 905.821.4001, www.patheon.com

**Single-Use Bioreactors for Mammalian Cell-Culture Applications**

EDM Millipore’s Mobius CellReady 200-L bioreactor is designed to expedite the process of bringing biological drugs to market. The machine integrates several features that are intended to provide ease of use, reliability, and operational flexibility. The bioreactor’s hardware includes on-board automation, which provides an ergonomic operator interface.

The Mobius SensorReady technology offers the flexibility to configure process monitoring at the point of use, thus reducing the need to customize bioreactor process containers and enabling easy integration of new sensor technologies. The rigid base and top panel feature of the bioreactor process container are designed to facilitate installation. The bioreactor is available as a complete, turn-key system or as a modular system to integrate with the user’s platform of choice. The bioreactor contains a working volume of 40–200 L, which allows it to function as both a seed and production vessel, and its standard design is optimized for the cultivation of mammalian cells in suspension.

EDM Millipore, tel. 800.548.7853, www.millipore.com

**Peristaltic Pumps Feature User-Friendly Applications**

Wheaton’s UniSpense Pro and OmniSpense Elite are designed to simplify and accelerate laboratory-throughput small filling operations. The devices also can dispense or aspirate multiple aliquots. The pumps are operated by an icon-driven interface that features a large display screen to enhance visibility and clarity. The systems are operated with a backlit 5-in. liquid crystal display with a chemical-resistant keypad, and options are displayed as large icons for quick operation and easy recognition in any language.

The pumps’ angled, polarized display is intended for use under a fume hood or biological safety cabinet. The pumps also contain a single intuitive calibration screen, designed for user-friendliness, that walks the operator through the process stepwise, thus eliminating scroll-through menus and the need for instruction manuals. In addition, the OmniSpense Elite and UniSpense Pro can be outfitted and programmed for specific processes. Once saved, these programs can be recalled easily, thus ensuring a quick application turnaround. Wheaton, tel. 800.225.1437, www.wheaton.com
Final Word – Continued from p.50

allows the development community to capitalize on opportunities to extend the reach and depth of our programs. USAID’s Global Development Alliance (GDA) is a premiere model for public–private partnerships, helping to significantly expand and deepen the impact of development assistance by linking US foreign assistance with the resources, expertise, and creativity of private sector partners. Since 2001, USAID has formed more than 900 alliances with over 1,700 distinct partners to leverage more than $9 billion in combined public and private resources. Across industry and sector, USAID is working in partnership with both global and local corporations to increase our reach and the effectiveness of development projects.

BioPharm: Some goals of the administration and of USAID are to increase access to health-care and treatment in developing nations, shorten the time of getting new vaccines to market (moving a 15–20 year timeframe closer to 1–5 years), and accelerating scale up of drug development. In what ways is USAID working to achieve these goals? Are there other important goals on USAID’s agenda in terms of global health efforts?

Batson: One of the major obstacles to providing timely and quality treatment in the developing world is the inability to access health facilities. The reasons for this are many. Often times the nearest clinic is simply too far from the community where an individual lives. Other times the costs of services are too high or social norms prohibit women from seeking the care they so desperately need.

Through the Global Health Initiative, we are working to integrate healthcare services, so that when a woman travels to a clinic to receive treatment for HIV, she doesn’t have to travel to another clinic for pediatric services for her child. We are also working to train and empower community health workers who bring critical health services directly to the communities. The idea of offering health services at the community levels is critically important when you consider that 80% of people in the developing world will likely never set foot in a health facility.

The most transformative technology at our disposal, vaccines, ensures protection against killer diseases, whether children are immunized by pediatricians in the US or by health workers in rural clinics in Africa. By making quality vaccines available at affordable and sustainable prices, manufacturers are contributing to...
an international commitment to protect more children. If we expand the coverage of existing vaccines and introduce new vaccines against pneumonia and diarrhea, we can save the lives of 4 million children over the next five years.

**BioPharm:** How can new drug products, including vaccines, be better introduced to developing populations? What are the key priorities in terms of advancing technology (e.g., meeting transportation or distribution challenges)?

**Batson:** Countries need to know how best to use data to find their greatest numbers of missed children and target those children with optimal approaches whether that means outreach, quarterly child health days, school-based approaches or targeting indigenous populations.

Distribution and cold-chain challenges vary from country to country and in some larger countries, state to state. Clearly countries have identified cold chain as a rate-limiting step with regard to new vaccine introduction. The supply chain has largely been undervalued and many countries do not have an adequate record of the status of cold chain equipment, maintenance requirements, and trained logisticians.

**BioPharm:** What can industry expect going forward in terms of working with USAID to get its new products or vaccines to developing nations? What type of assistance may be provided and what are the timeframes?

**Batson:** USAID is going to continue to focus on what we do best. That is we will continue to work with our partners at global, regional and country levels to provide varying support. We work with WHO and UNICEF, as well as our other donor partners, GAVI, the Gates Foundation, and most importantly, countries themselves. USAID is not the only partner to industry with regard to getting programatically suitable vaccines developed and used in developing countries. Together, the US government makes tremendous investments in vaccines from basic research and development to field level strengthening of immunization programs.

**BioPharm:** Can you talk about the large commitment the US recently made to GAVI and what this will achieve? Does USAID have any other financing programs in the pipeline?

**Batson:** To reiterate, one of the most transformative technologies at our disposal is vaccines. The United States’ coordinated support for GAVI complements the efforts of the National Institutes of Health, the Centers for Disease Control and Prevention, and USAID in the research, development and sustained use of vaccines in robust, country owned immunization programs.

The US commitment leverages the billions of dollars that other donors have committed to GAVI, multiplying the impact of our funding more than eight-fold, and allowed GAVI to negotiate a price reduction of 67% on rotavirus vaccines so more of the world’s most vulnerable people will be protected against preventable diseases.

Combined with other donors, our funding will enable the Alliance to provide countries with sufficient amounts of programatically suitable vaccines to immunize an additional 243 million children in the poorest countries with vaccines against pneumococcal disease, rotavirus, Haemophilus influenzae type b (Hib), hepatitis B, meningitis A, and yellow fever, and ensure the complete roll-out of pentavalent vaccine. Experience delivering vaccines to expanded target populations could also serve to strengthen immunization programs to put the world in a position to save more lives with potential future vaccines against malaria, tuberculosis, and HIV.

**BioPharm:** Once a new drug or vaccine is introduced a developing-nation market, what are USAID’s goals for ensuring that the country can sustain the administration, purchase, and distribution of that product?

**Batson:** We strongly support the GAVI co-financing strategy that requires all countries to make a co-payment for every dose of vaccine provided to that country through GAVI procurement. The relatively recent revisions to the GAVI’s co-financing policy requires a larger payment for countries closer to ‘graduation.’ We want countries to be mindful of their financial obligations but we want to continue working with our partners on the expansion of the evidence base for decision making so that when countries have to make hard decisions about how to spend their money, they will realize the tremendous health impact vaccines have.

**BioPharm:** Many individuals seem to be opposed to global health efforts compared with say, focusing on the US healthcare system at home. What can be done to overcome this perspective?

**Batson:** We recognize that global health is vital to our national security. Improving the health of people in the developing world drives economic growth, fights poverty, and strengthens families, communities and countries. Investing in the health of people in developing countries reduces the instability that fuels war and conflict. Fighting global disease directly protects our health in the United States because infectious diseases know no borders.

A continued effort to communicate the value and incredible return on investment from our global health efforts will be key to maintaining this support through the uncertain economic times ahead. ◆
President Obama launched the Global Health Initiative in May 2009 to introduce an integrated approach to the government’s investments in global health. The initiative involves programs of the US Agency for International Development (USAID), the Department of Health and Human Services (HHS), PEPFAR, and the Peace Corps, among other agencies. Innovation and development are key components of the initiative’s and the administration’s goals. BioPharm International spoke with Amie Batson, appointed by Obama to lead USAID’s role in the initiative, about progress thus far and plans forward.

BioPharm: Why are innovation and development such a big push now compared with past years?

Batson: At USAID, we realize the benefits of investing in innovation for global health go well beyond improvements in health. Some of the greatest advances in development have come from extending the reach of innovative breakthroughs to those who lack access health facilities. We are looking to build stronger partnerships with the development and scientific communities to support the creative thinkers who are developing the next generation of health technologies capable of reaching more people at reduced costs to maximize impact.

USAID Administrator Dr. Rajiv Shah has stated on several occasions that the largest opportunities to improve human health and the human condition do not lie in optimizing services to the 10–20% of people in the developing world who have access to world-class health facilities. They lie in extending our reach to the 80–90% of people who do not.

BioPharm: What are some examples that have come about from the initiative to date?

Batson: In 2011, at the Bill and Melinda Gates Malaria Forum in Seattle, USAID welcomed the initial news of the Phase 3 efficacy trial that confirmed the RTS,S malaria vaccine is safe and effective, and could eventually add to our present package of malaria control interventions saving more lives among young children in Africa.

In 2010, USAID proudly announced the first-ever proof of concept that a microbicide gel can effectively and safely reduce the transmission of HIV from men to vulnerable women, placing the power of HIV prevention in the hands of women.

The Global Alliance for TB Drug development is bringing a new drug combination to Phase III trials that could cut the duration of treatment by half and help overcome MDR-TB.

With each advancement, we come closer to delivering more effective aid at a lower cost. In tough economic climates like this one, the question we should all be asking is what tangible benefits we will see for each dollar spent. There is no question that investing in the health technologies of tomorrow will reap incredible returns on our original investment, and in lives and money saved.

BioPharm: USAID Administrator Shah has spoken about how the agency is trying to improve its relationship with the private industry to make communication easier and less bureaucratic. What is USAID looking to do in this regard? What types of new partnerships is the agency forming?

Batson: Cultivating a productive investment environment will require partnerships with a range of stakeholders in donor and host countries, including the private sector, civil society organizations, research institutions, foundations, and emerging and traditional donors. Our partnerships should reflect new models such as South–South and trilateral cooperation, and include meaningful roles for civil society and the private sector.

Leveraging the collective resources of partners through public–private partnerships

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The Parenteral Drug Association presents...

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  - The Future of Personalized Medicine – Challenges Ahead, Ted Love, MD, Executive Vice President, R&D and Technical Operations, Onyx Pharmaceuticals

- Plenary Session Two:
  - The Future of the Biopharmaceutical Industry, David Urdal, Chief Scientific Officer, Dendreon
  - Financial Analyst Perspective on the Pharmaceutical Industry, Barbara A. Ryan, Managing Director, Research Analyst, Deutsche Bank Securities, Inc. (invited)
  - Student Call for Posters – Abstracts Due February 6, 2012

- Closing Plenary Topics:
  - Manufacturing Opportunities and Challenges in the Next 10-20 Years, Matt Croughan, Professor, Keck Graduate Institute of Applied Life Sciences
  - Emerging Regulatory Expectations, Emily Shacter, PhD, Chief, Laboratory of Biochemistry, CDER, FDA

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