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April 2012

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The Science & Business of Biopharmaceuticals

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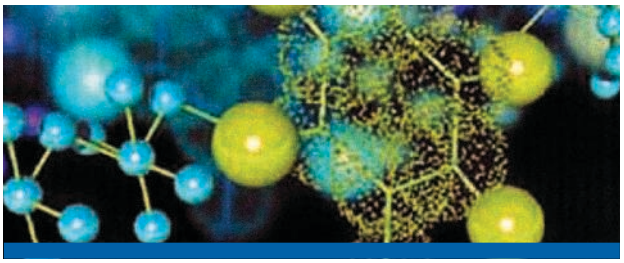

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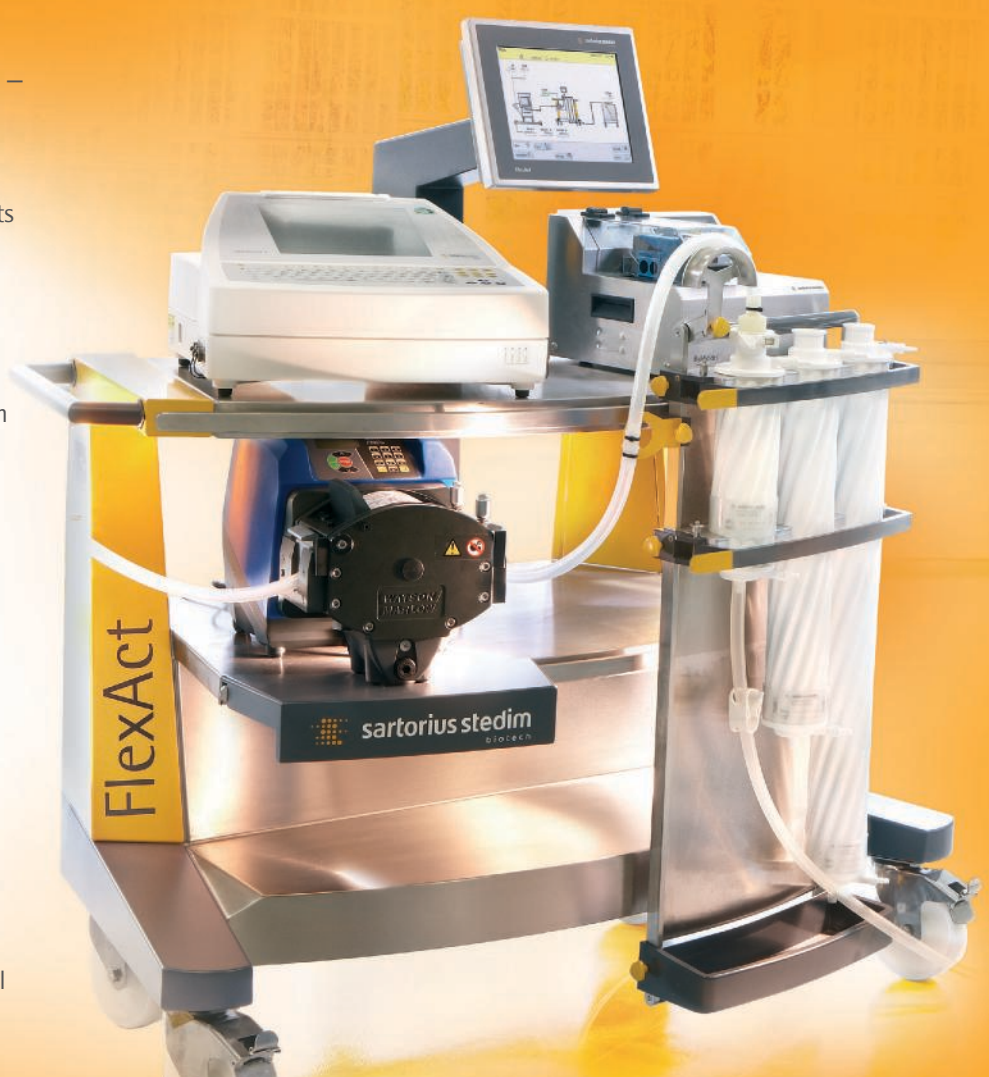

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BioPharm INTERNATIONAL

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PEER-REVIEWED FEATURE

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BioPharm International ISSN 1542-166X (print); ISSN 1939-1862 (digital) is published monthly by Advanstar Communications, Inc., 131 W. First Street, Duluth, MN 55802-2065. Subscription rates: $76 for one year in the United States and Possessions; $103 for one year in Canada and Mexico; all other countries $146 for one year. Single copies (prepaid only): $8 in the United States; $10 all other countries. Back issues, if available: $21 in the United States, $26 all other countries. Add $6.75 per order for shipping and handling. Periodicals postage paid at Duluth, MN 55806, and additional mailing offices. **Postmaster** Please send address changes to *BioPharm International*, PO Box 6128, Duluth, MN 55806-6128, USA. PUBLICATIONS MAIL AGREEMENT NO. 40612608, Return Undeliverable Canadian Addresses to: Pitney Bowes, P. O. Box 25542, London, ON N6C 6B2, CANADA. Canadian GST number: R-124213133RT001. Printed in U.S.A.

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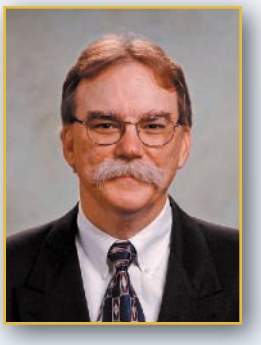

Richard Johnson is president of the Parenteral Drug Association (PDA), Johnson@pda.org.

The confluence of science, technology, and regulation will provide our industry with the guidance to move forward.

PDA Tackles Changing Industry Times

The year 2012 will be challenging for the biopharmaceutical industry. The marketplace is shifting, bringing unique challenges to manage and explore. Exciting advancements like new drug discoveries and therapies, the increasing importance of biotechnology, growing global demands for better healthcare, and the changing demographics of our societies are taking their place at the global table. At the same time, there is a confluence of economic, political, and regulatory changes influencing business models and mandating new and innovative practices. Some key drivers that our industry is facing include:

- increasingly complex supply chains and outsourcing models
- patent erosion
- a continued focus on cost management
- the rising importance of emerging biopharmaceutical markets.

As a leading nonprofit association, the Parenteral Drug Association (PDA) and its Board of Directors have been hard at work implementing a strategic plan that will guide the association forward. PDA will continue to focus on "Connecting People, Science, and Regulation" in an industry where "change" is the hallmark of our future. Specifically, the association plans to: focus resources to deliver more PDA technical reports, technical surveys, and guidance; continue signature meetings such as our annual PDA/FDA Joint Regulatory Conference (September 2012); introduce new "hot topic" conferences and workshops on subjects such as glass quality; expand global training activities (60 are currently offered worldwide); and expand synergy to work with global regulatory agencies to enhance pharmaceutical science and advance patient healthcare.

The 66th PDA Annual Meeting, Apr. 16–18, 2012, in Phoenix, AZ, will focus on many of these themes. Industry and regulatory speakers will present on "Manufacturing Innovation: Achieving Excellence in Sterile and Emerging Biopharmaceutical Technology." Major educational tracks include: Innovation and Productivity in Large Scale Manufacturing; Personalized Medicine/Cellular Therapeutics; and Control Strategies for Biopharmaceuticals.

The conference will also offer training courses on Reprocessing of Biopharmaceuticals; Recommended Practices for Manual Aseptic Processes; Implementation of Quality Risk Management for Commercial Pharmaceutical and Biotechnology Manufacturing Operations; Process Simulation Testing for Aseptically Filled Products; and several others.

The industry business drivers noted above will impact how we work and interact. The confluence of science, technology, and regulation will provide our industry with the guidance to move forward, improve patient healthcare, and create future business models needed to survive.

I look forward to your feedback, and would like the opportunity to welcome you to our community. ♦

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Bob Stewart is Industry Vice President of INTERPHEX, rstewart@reedexpo.com

Collaboration can begin with a conversation.

It Happens at INTERPHEX

We may be living in a time of global economic challenges, but it's also a time in which the bio/pharmaceutical industry continues to propel itself forward, navigating its way through maturing and emerging markets, compliance needs, and outsourcing options, all while keeping its eye on long-term development and today's complex requirements. These actions are no small undertaking, but seeking to solve health problems across populations demands such an approach.

It is in serving this industry that INTERPHEX has established a history of leadership in bringing together minds, materials, and services every year, and it is because of this that we are also propelling ourselves forward in 2012.

For starters, we are introducing a re-engineered conference, taking place May 1–3 at New York City's Javits Center. This year's conference has grown to include tracks, special sessions, technical workshops, and keynote presentations, resulting in the event's largest program component ever. At its heart is a five-track set of sessions designed to reflect the cross-functional team approach that firms use to move a drug to market: Regulatory Quality Assurance/Quality Control; Product Development; Facility & Process Design; Manufacturing & Packaging; and Supply Chain. Each track is chaired by a member of the 2012 INTERPHEX Advisory Board and will feature senior-level presenters to share the latest achievements in each stage. The Board has been invaluable in raising the bar on conference criteria, enabling us to present a more rigorous curriculum and to bring in speakers from organizations such as FDA, NASA and the US Department of Commerce, as well as from more international firms and leading companies.

Complementing the tracks will be technical workshops, led by representatives of companies that understand what works because they have successfully done it. Participants will include Pall Life Sciences, Glatt Air Technologies, Fette Compacting America, Bosch, OSO Pharmaceuticals, GE Healthcare, STERIS, Thermo Fisher Scientific, and EMD Millipore. These workshops will be followed by special sessions.

A higher emphasis on case studies will be prevalent in this year's educational sessions. Case studies can also be found in the technology floor tours, focusing on advanced aseptic, biologics, and oral solid-dosage form manufacturing. Expanded access is another key theme to INTERPHEX 2012. The conference's heightened level of education will have a greater reach: the Thursday sessions, keynote presentations, floor tours, and technical workshops will be open to all badge holders, welcoming both conference and exhibits-only attendees. Finally, we focus on a continued partnership with the International Society of Pharmaceutical Engineering (ISPE). This year marks ISPE's 15th year as the major INTERPHEX sponsor and, as part of that, representatives of the Category and Special Recognition award winners in the 8th annual Facility of the Year Awards (FOYA) program will attend and discuss their successes in innovation, execution, integration, excellence, and collaboration in the only joint appearance they will make outside of ISPE's Annual Meeting in November.

On the exposition floor, hundreds of the industry's suppliers will be present, representing more than 650 suppliers and 1000 product lines to fill the zones of Facilities, Manufacturing & Packaging, Automation Systems & Controls, and Sourcing & Services. They'll bring their latest and best offerings and their brightest people, who will be there to meet with attendees who have sourcing needs.

Facing a challenging global economy and significant industry changes, we often lose sight of the basics. Particularly in this age of communications leveraged by networks, wireless devices, and a worldwide web, we have to remember that people have not lost the need to connect, face-to-face, to teach, to learn, to do business, and to know each other better. Personal collaboration is crucial to the industry INTERPHEX serves, and collaboration can begin with a conversation, with a meeting. Our goal this year has been to provide an even greater marketplace and a knowledge center where even more professionals can come together to share even more innovation and problem-solving. ♦

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Discovery Pipeline

FDA Approves First Allogenic Cell-Based Therapy

Dendreon made headlines in 2010 with the approval of its autologous cell-based vaccine, Provenge. An autologous therapy such as Provenge uses the patient's own cells to create the therapeutic. On Mar. 9, 2012, FDA announced the approval of the first allogenic cell-based therapy, one that uses cells unrelated to the patient to create the therapeutic. The therapy, called GINTUIT, is made by Massachussetts-based Organogenesis, and will be used to treat mucogingival conditions in adults. Mucogingival defects are soft tissue defects of the mouth involving both the attached gums (i.e., gingiva) and other oral tissue at the juncture with the gingiva. These conditions may be caused by injury or infection, or may be anatomic defects.

GINTUIT is a cellular sheet that consists of two layers. The top layer contains human keratinocytes, a type of skin cell that makes up the outer surface of the skin. The lower layer contains human fibroblasts, human extracellular matrix proteins, and bovine collagen. In clinical studies, GINTUIT was shown to generate a significant amount of keratinized oral soft tissue that better matched the color and texture of the patient's surrounding tissue compared with tissue derived from traditional palatal grafting procedures.

The exact mechanism by which GINTUIT works is not known. However, it is thought that cytokines and growth factors secreted by the cells in the therapy promote wound healing and tissue regeneration. Dr. Michael K. McGuire, the lead investigator of the pivotal trial said in a company press release, "Delivering a construct with living cells that can generate new tissue indistinguishable from what nature intended is unprecedented and exciting." Organogenesis expects that GINTUIT will be commercially available via a controlled market release beginning in the summer of 2012 and available to the broader US market in 2013.

—Amy Ritter

Report from China

China's drug-distribution network has been a mess for years, but government reforms and industry focus are unveiling new opportunities for market order and growth.

Panoramic images/Getty Images

In recent years, the Chinese government has been ramping up efforts to improve drug distribution throughout the country. In its 12th Five-Year Plan (2011 to 2015), the government encourages re-organization, as well as mergers and acquisitions to improve the existing network, which is fragmented and often inefficient.

China's drug-distribution system has undergone development over the years. Prior to the reforms, state-owned wholesalers purchased drugs directly from manufacturers, resulting in bureaucratic order and lack of competition. When the country opened its doors to the world in 1978, manufacturers were given the go-ahead to sell drugs directly to pharmacies and hospitals. Although citizens have easy access to medicines today, drug distribution remains unregulated and users often obtain drugs from unknown or unauthorized sources.

Drug manufacturers and distribution companies therefore continue to face daunting challenges in the Chinese market. To begin with, China is a huge country spanning 9.6 million kilometres with an estimated population of 1.3 billion, of which 700 million are located in difficult-to-reach rural areas. The government's aim is to narrow the gap of healthcare offerings between the urban and rural areas. However, Vice Health Minister Huang Jiefu cautions that "the gap will probably not be closed in the next 30 years."

There is also the problem of layers of distribution levels; drug prices rise at each level, which leads to higher distribution costs. Yvonne Wu, national leader, life sciences and healthcare of Deloitte China, says, "It is common that top-level distributors double up as second-level distributors. Having established good relations with hospitals of certain classes at various locations, they have different business focuses and strategies. Therefore, it becomes complicated to segregate and pick the right distributors by using level classification."

Given this situation, it is not surprising that the government supports integration and consolidation of its drug-distribution network. Wu comments that, "this will contribute to the emergence of market leaders, support local pharmaceutical companies to market their products beyond China, and escalate the market position of the country."

Huang Donglin, an industry analyst in the healthcare division of Frost & Sullivan China adds, "The gross margin of drug distribution has decreased over the years. Companies need efficient management, higher service quality and size to develop the business. And integration can only be achieved through in-depth organization and business adjustment."

Well-established distributors have already adopted this approach. In 2010, Sinopharm Group, based in Haidian, Beijing, became the first to own distribution channels in all Chinese provinces by acquiring small and mid-size companies. In January 2011, Shanghai Pharma Group acquired CITIC Pharma to enter the northern China market. Newcomers such as Cardinal Health, based in Ohio, acquired Hong Kong-based Yong Yu (also known as Zuellig Pharma China) for $470 million in 2011. Cardinal also opened a logistics center in Shanghai to expand its business horizon in the country.

The government's commitment to overhaul China's drug-distribution network has become quite transparent as a means to lower drug prices. Last September, it reduced the retail price ceiling of 82 pharmaceutical drugs by an average of 14%. The Ministry of Public Security recently ended a campaign involving 1280 investigations across 170 cities in 29 provinces and autonomous regions to ensure drug safety. There is also a need to ramp up digitalization of drug supervision. The plan has also included unified code management for approved drugs and electronic supervision of all drug types.

China's five-year plan includes developing one to three large-scale leading distributors with annual sales of more than $15.9 billion. There is also a plan to establish 20 regional distributors with annual sales of more than $1.6 billion by 2015. The leading domestic players (i.e., Sinopharm Group, Shanghai Pharmaceutical, and Guangdong Jiuzhoutong Pharmaceutical) held less than 20% of the drug-distribution market share in 2009.

Wu says, "The plan may not have rigid performance indicators but it has identified six entrance thresholds. For example, a distributor's warehouse must be 50,000 square metres and cover 80% of its hospital network. Other requirements involve areas of transportation vehicles, information systems, e-commerce, and annual sales volume."

Interestingly, online purchasing of drugs is gaining popularity on Chinese soil. Wu comments that online drug sales may still be in its infancy, but "it is expected to be a low-cost sales channel supporting major sales channels in the coming years." The online purchase option has also made the drug-procurement process for healthcare institutions easier and faster, a spokesperson at the drug purchasing department of Anhui province adds.

China's five-year plan includes developing one to three large-scale leading distributors with annual sales of more than $15.9 billion.

In fact, many provincial governments, including the Beijing Municipality and the Guizhou province, are promoting the use of online platforms. At the end of January 2011, Beijing's 167 medical institutions placed 289,423 online orders and 85 drug-distribution companies had fulfilled them. The online platform registered a 9858 medicines bought online with daily transaction value of $14.86 million.

Looking forward, there are many opportunities for industry players in the drug-distribution business. The sector is expected to maintain an annual growth rate of 8% during the next five years to raise total sales to more than $1.2 trillion by 2015, up from $773 billion in 2009.

However, drug-distribution companies will need to streamline their processes to strengthen their competitiveness in the market. Huang explains, "Distribution companies need to set up new operational strategies and optimize management structure to serve clinical demands. Ultimately, service quality and ability affect the competitiveness of a distribution company. Because it acts as a bridge between manufacturers and users, it must build on its range of value-added services to benefit both up and downstream parties."

—Jane Wan is a freelance writer based in Singapore.

Boehringer Expands Biomanufacturing Capacity in Europe

Boehringer Ingelheim (BI) has announced in a press release the expansion of its biopharmaceutical manufacturing capabilities at its plants in Biberach, Germany, and in Vienna, Austria.

The expansion will include cell-culture and microbial-fermentation capacity and support cell-line and process-development services for BI's contract manufacturing business. BI has invested approximately EUR 17 million ($26.8 million) to expand cGMP cell banking, process science, cell-line development, and quality laboratories at the two sites.

BI expects to use the expanded resources for services that include monoclonal antibody development, product development using BI's proprietary high-expression systems, and proprietary plasmid DNA platform. In addition, the facilities will support collaborations with Pfenex on *Pseudomonas fluorescens* bacterial expression technology and with VTU Technology on *Pichia pastoris* yeast expression technology.

In the company release, Dorothee Ambrosius, senior vice-president of Biopharmaceuticals Global Process Science, says, "This is another milestone within our contract manufacturing strategy securing technology leadership and towards increased flexibility and customer orientation."

—Amy Ritter

Lilly Invests EUR 330 Million in Biopharmaceutical Manufacturing

Eli Lilly is to invest $443.2 million at its Kinsale campus in Ireland to create a brand new biopharmaceutical commercialization and manufacturing facility. The investment will lead to 200 new jobs, as well as a further 300 construction roles during the building process.

The facility is planned to be approximately 24000 square feet and will be produce treatments for illnesses such as cancer and diabetes. In a press release, Lilly's senior vice-president of global API and dry product manufacturing, Paul Ahern said, "This investment is part of Lilly's planned growth strategy and proof of our confidence in Lilly's pipeline of new products, many of which are derived from biotechnology."

Eli Lilly first established its presence in Kinsale in 1981 and the facility makes APIs for several of the company's products. The latest announcement marks the second significant investment that the company has made at the site in recent years. In 2006, the company committed to invest $395.2 million in a biopharmaceutical and new-product commercialization facility. The new facility came on line in 2010, but is still undergoing start-up activities. It is expected to manufacture commercial products in late 2013.

Ireland's investment agency, IDA Ireland, worked closely with Lilly to attract the new investment. According to Ireland's Minister for Jobs, Enterprise and Innovation, Richard Bruton, the government has recently outlined a range of measures that will be taken in 2012 to target high-end manufacturing and the health and life science sectors for growth and job creation.

Several other pharmaceutical companies have invested in Ireland recently. Most recently, Abbot Laboratories announced an approximate $112-million investment at its manufacturing facility in Sligo. And in September, Pfizer and Merck Sharp & Dohme invested $194.8 million and $134.3 million in Irish pharmaceutical operations, respectively.

—Stephanie Sutton

EMA Announces Electronic Pilot Program

EMA has launched a pilot program for submitting centralized marketing authorization applications electronically. The pilot began on Mar. 12, 2012, and is expected to be active for four months. During this period, companies will be able to apply for initial marketing authorization applications for human medicines, and submit variation and renewal applications for human and veterinary medicines using an interactive PDF form.

In a press statement, EMA explained that the pilot is a step towards using electronic applications as standard, using the Electronic Common Technical Document (eCTD) format. Electronic applications are expected to simplify and accelerate the application process by improving data quality and consistency during data entry, providing access to data in XML format, and integrating application data with controlled terminology.

Depending on the success of the pilot, the PDF forms may become an alternative, as well as the recommended format for submitting eCTD applications to EMA. The forms were developed in collaboration with EMA, European Commission services, and medicines regulators in EU member states, and their content is identical to that of the current application forms published by the European Commission in EudraLex, Vol. 2.

Details on how to participate are described in the EMA's electronic application forms pilot guidance.

—Stephanie Sutton

GE Healthcare to Acquire Xcellerex

On Mar. 7, 2012, GE Healthcare announced an agreement to acquire Xcellerex, a supplier of manufacturing technologies for the biopharmaceutical industry, for an undisclosed amount.

According to a press release, the acquisition will allow GE Healthcare to expand its offering of products and services for the manufacture of biopharmaceutical products such as recombinant proteins, antibodies, and vaccines. Xcellerex develops and produces turn-key biomanufacturing systems and production-scale bioreactors based around single-use components, including single-use bioreactor systems that are complementary to GE Healthcare's products and range of media for cell culture.

Expanded capabilities in product development and marketing, will offer significant customer benefits.

The companies believe that the strong strategic fit between the two companies, combined with expanded capabilities in product development and marketing, will offer significant customer benefits.

Nigel Darby, vice-president of BioTechnologies, and chief technology officer of GE Healthcare Life Sciences said in the release, "GE and Xcellerex share the vision that an integrated approach, where we can help customers optimize every stage of their manufacturing process, has the potential to increase production flexibility and to deliver higher yields of finished product while reducing time to market. With the global focus on spiraling health costs and the need for sustainable healthcare, these are critical issues for the industry."

Guy Broadbent, president and CEO of Xcellerex, adds, "The integration of Xcellerex's products with GE Healthcare's complementary capabilities in upstream and downstream bioprocessing will help bring great benefits to our customers."

—Amy Ritter

When purity is key…

Manufacturers Wrestle with Drug Abuse and Critical Shortages

Soaring opioid use creates challenges for new drug development and supply-chain control.

The United States is caught in an epidemic of prescription-drug overuse and abuse, and federal enforcers are revving up forces to counter illegal diversion of approved drugs. Nearly 7 million Americans abuse psychotherapeutic drugs, according to a survey by the Department of Health and Human Services (HHS), and prescription drug abuse now exceeds that of cocaine and heroin. Consequently, manufacturers of opioids and other painkillers, along with prescribers and drug distributors, face increased scrutiny from the Drug Enforcement Administration (DEA) and other regulators seeking to monitor drug distribution and prescribing more aggressively. A House Energy and Commerce subcommittee held hearings in April 2011 and again in March 2012 to examine how DEA is tracking and preventing inappropriate prescription-drug use, the effectiveness of state prescription drug-monitoring programs, and how well manufacturers, distributors and pharmacists prevent illegal diversion. Subcommittee Chair Rep. Mary Bono Mack (R–CA), has pressed for policies to aggressively curb access to painkillers and anxiety drugs more severely since the suicide of her son related to oxycontin abuse.

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Of the thousands of pharmaceuticals approved by FDA for US marketing, about 250 are regulated by the the Controlled Substances Act of 1970 (CSA). Some 80 drugs with high abuse potential but important medical uses fall under schedule II, including sleep aides, diet pills, antidepressants, psychiatric drugs and antihyperactive therapies, as well as painkillers. Another 150 drugs have relatively low abuse potential and are in schedules III–V with minimal restrictions, while more than 130 schedule I drugs are dangerous and not approved for any uses.

> FDA officials advise manufacturers to address scheduling issues early in drug development to facilitate the review process.

DEA and other federal and state agencies have responded to the sharp rise in abuse of opioids and other legal drugs as part of the 2011 Prescription Drug Abuse Action Plan released last year by the White House Office of National Drug Control Policy. DEA agents have been closing down illegal online pharmacy sites and rogue pain clinics, particularly in Florida, that dispense thousands of prescriptions for pain medicines. A main DEA thrust is to target drug wholesalers and distributors that fail to detect and halt diversion; DEA recently moved to shut down a Cardinal Health distribution facility and four pharmacies in Florida allegedly for overlooking highly excessive oxycodone orders.

Recent legislation also authorizes more aggressive efforts to remove leftover prescription drugs from family medicine cabinets, and DEA is holding another national "take-back" initiative this month, aiming to collect tons of expired or unwanted medicines for proper incineration. Brand and generic-drug manufacturers support these efforts, but are

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wary of proposals from the state of Washington and a California county that call for manufacturers to foot the bill for more extensive collection of leftover prescriptions.

SEEKING DEA APPROVAL

Another concern for industry is that added requirements for bringing schedule II therapies to market can delay patient access to new drugs by six months or more. DEA also sets annual quotas on production of controlled drug substances, a factor that may aggravate shortages of certain widely used drugs.

FDA assesses about one-third of new drug applications (NDAs) to see whether they warrant additional scheduling review by the DEA, noted Douglas Throckmorton, deputy director of the Center for Drug Evaluation and Research (CDER), at a February 2012 seminar on controlled substance regulation sponsored by the Food and Drug Law Institute (FDLI). CDER's Controlled Substance Staff (CSS) determines whether DEA should evaluate the product further, which can lead to a complex scheduling process after FDA approves the NDA.

This DEA review, for example, delayed marketing 11 months after FDA approval in 2008 of Esai's sedation medication Lusedra (fospropofol). GlaxoSmithKline had to wait nearly six months to market its new epilepsy drug Potiga (ezogabine), despite early communication with DEA on the product's unique features. DEA scheduling "is a big black box for industry," observed Esai regulatory policy executive Ginny Beakes-Read, with no timelines for its actions and recommendations.

FDA officials advise manufacturers to address scheduling issues early in drug development to facilitate the review process. Sponsors need to characterize whether a drug produces positive psychoactive effects, such as sedation, euphoria and cognitive distortion, explained CSS pharmacology team leader Silvia Calderon-Gutkind. NDAs should clearly identify abuse liability—or its absence—through evaluation of chemical properties, pharmacological and pharmacokinetic characteristics and clinical data relevant to abuse.

CDER is working to improve its internal assessment process for controlled substances and to negotiate a memorandum of understanding with DEA to facilitate exchange of confidential information on new drugs earlier in the review process. FDA issued draft guidance last year on how manufacturers should assess the abuse potential of new drugs, and advice on developing abuse-deterrent formulations is expected this year.

Although there's great interest in abuse-resistant patches or capsules, so far none have emerged that are "truly effective," said Gary Boggs, executive assistant in DEA's Office of Diversion Control, at the FDLI meeting. Manufacturers look to add antagonists or change formulations to improve resistance, but DEA wants data to show that it works and warrants "down-scheduling" to a DEA category that carries less regulation of production quantities, physical security, prescribing, and distribution.

Ultimately, better science may establish a clearer roadmap for assessing drug pharmacology and clinical studies related to abuse issues, particularly for new drugs with novel mechanisms of action. Criteria for identifying and reporting adverse events related to prescription-drug abuse also could provide safety data that supports changes in controls, as would efforts to increase prescriber and patient education on the appropriate use of opioids and abused drugs.

AGGRAVATING SHORTAGES

DEA quotas on active ingredient supplies and production volume for schedule II drugs also have drawn scrutiny as factors contributing to shortages in critical drugs. Manufacturers claim that such controls have reduced supplies for treatments for attention-deficit/hyperactivity disorder (ADHD), which often contain amphetamines. DEA can amend aggregate drug production quotas during the year when there is a "legitimate need," explained Boggs. But he noted that it's hard to quantify such need, and the amendment process involves a lengthy comment-and-rulemaking procedure. FDA has been able to work with DEA to prevent shortages in several cases, notes Valerie Jensen, associate director of CDER's drug-shortage program, and Congress may modify the DEA quota-setting policy as part of legislation to address drug shortages in development on Capitol Hill.

FDA is moving aggressively to deal with shortages of critical drugs on all sides, as witnessed in recent actions to ensure access to two key cancer medicines. Commissioner Margaret Hamburg announced at a February 2012 briefing that FDA remedied a serious shortage in a version of cancer drug Doxil (doxorubicin hydrochloride liposomal injection) by authorizing Caraco Pharmaceutical Laboratories to temporarily import a replacement drug, Lipodox, produced overseas by India's Sun Pharma Global FZE. Serious manufacturing prob-

lems at contract supplier Ben Venue Laboratories, a division of Boehringer Ingelheim, dried up Doxil production for Johnson & Johnson's Janssen Products, leaving physicians desperate for supplies of this important cancer and AIDS treatment. FDA officials emphasized that import of this unapproved foreign drug will be a temporary, limited arrangement and was authorized only after the agency evaluated Sun to ensure the quality and safety of the product.

FDA also resolved a critical shortage of methotrexate, also related to Ben Venue production problems, by expediting approval of a manufacturing supplement from APP Pharmaceuticals and release of thousands of vials produced by Hospira. Preservative-free methotrexate is needed to treat children diagnosed with acute lymphoblastic leukemia as well as other serious conditions. FDA also is working with Mylan and Novartis' Sandoz Pharmaceuticals to increase their methotrexate production.

Hamburg said that FDA is dealing with these problems by expanding its drug-shortage team, providing guidance to industry on drug shortage notification procedures, and backing legislation to expand required reporting. By working closely with generic- and brand-drug makers, FDA has prevented 114 shortages since October 2011, Hamburg pointed out.

Yet, the commissioner also noted in a speech to the annual meeting of the Generic Pharmaceutical Association in February that the majority of drug shortage problems are related to compliance issues affecting product safety and quality. On almost the same day that APP announced expanded methotrexate production, FDA issued a scathing Warning Letter citing the company for significant manufacturing violations at its Grand Island, NY. facility, primarily related to heparin production. Hospira was able to ship some 65,000 vials of methotrexate in February because it obtained additional supplies of active ingredient and invested hundreds of millions of dollars in extensive plant remediation efforts to resolve serious quality manufacturing issues cited multiple times by FDA.

Manufacturers of medically necessary drugs "must invest in their manufacturing facilities," Hamburg advised the generic-drug manufacturers, noting that "quality is crucial for all products," and that visible shortages involving generic drugs could lead to public "to equate generics with quality concerns." ◆

Regulatory Roundup

Budget battles

In addition to relying on ever-greater user fees to finance FDA operations ($2 billion in fees on a $4.5-billion budget), the Obama administration's spending plan for fiscal year 2013 takes some heavy swipes at biopharmaceutical companies. The president proposes to lower the exclusivity period for innovator biologics to seven years from 12 and to ban brand-generic "pay-for-delay" settlements. There's also the Democratic favorite to extend Medicaid rebates to all low-income beneficiaries in Medicare Part D plans, which is calculated to cut spending by $156 billion over 10 years. John Castellani, president of the Pharmaceutical Research and Manufacturers of America (PhRMA), blasted these proposals in a statement as a counter to "Obama's many pronouncements to support innovation, advance biomedical research, promote job creation and control healthcare costs for seniors." Congressional Republicans rejected the Obama budget immediately, taking particular aim at the administration's request for another billion dollars to fund healthcare reform, along with the antipharmaceutical provisions.

Chinese suppliers

US regulators have expanded the so-called "import alert" list to include 14 more Chinese producers of heparin and related products, for a total of 22 Chinese firms linked to the heparin contamination crisis of 2008 and still unable to meet FDA standards for manufacturing and quality control. The move additionally aims to assure Congressional Republicans that FDA is serious about ensuring the safety of heparin products in the US.

FDA also aims to bolster its presence in China by seeking an additional $10 million in its FY 2013

Continued on p.20

Continued from p.19

budget to expand the scope of in-country inspections and staff. A new FDA report to Congress on its foreign offices and operations, as required by recent food-safety legislation, summarizes FDA overseas activities and interactions with regulatory authorities in China, India, Latin America, Europe, Africa and the Middle East, designed to build rapport and obtain important information on local production and regulatory operations.

Foreign corruption

Manufacturers are supporting a new mandatory code of conduct for dealing with doctors and other providers around the world, largely to offset charges of violating the US Foreign Corrupt Practices Act (FCPA) and similar laws set by other countries. Spurred by a rise in investigations and charges levied against pharma companies by US and foreign enforcement agencies, the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) has updated its ethical practice code to cover broader industry interactions with health professionals. Astra Zeneca CEO David Brennan, IFPMA president, said in a Mar. 1, 2012 statement, that the new policy can help industry "act with integrity and build trust." The code bans gifts and curtails entertainment to docs—and may save manufacturers in legal fees and fines: Johnson & Johnson paid some $70 million last year to settle charges of illegal payments overseas, and Serbia is investigating several bio/pharmaceutical companies for bribery and corruption.

Counterfeits

Counterfeiters continue to become more sophisticated, as demonstrated in the recent discovery of fake Avastin sold to doctors in California, Texas, and Illinois. Unfortunately for patients, this "lower-priced European alternative" of Avastin has no active ingredient (bevacizumab). FDA sent letters to 19 doctors instructing them to stop using this unapproved product and pointing out the dangers of purchasing critical medicines from unknown sources, in this case from Quality Specialty Products (also known as Montana Healthcare Solutions). The doctors evidently were attracted by a $1900 price tag on a drug that usually costs about $2400 from Roche's Genentech. The Avastin incident prompted the Senate to approve a bill stiffening penalties on drug counterfeiters, and further legislation may authorize a better drug tracking system to distinguish genuine medicines from fakes. In addition, the Institute of Medicine is preparing a report for FDA on ways to detect and prevent drug counterfeiting and adulteration, hoping for delivery by year-end.

Bioterrorism

Biotech manufacturers are cheering new legislation to strengthen the nation's response to public health emergencies, which provides added support for developing new medical countermeasures critical to such efforts. The US House or Representatives approved the Pandemic and All-Hazards Preparedness Act (PAHPA) in late 2011, and the Senate followed suit last month. The bill authorizes about $8 billion over five years to bolster detection and response to threats by the Centers for Disease Control and Prevention (CDC) and increases funding for countermeasure development and procurement. FDA also gets support for expert teams to provide technical assistance to manufacturers of vaccines, treatments and diagnostic tests important for responding to threats.

Recently issued key guidance documents

- Postmarketing Adverse Event Reporting for Medical Products and Dietary Supplements During an Influenza Pandemic (FDA Final Guidance)
- Size of Beads in Drug Products Labeled for Sprinkle (FDA Final Guidance)
- Q3C Impurities: Residual Solvents (FDA final recommendation based on ICH guideline)
- Drug Interaction Studies–Study Design, Data Analysis, Implications for Dozing, and Labeling Recommendations (FDA Draft Guidance)

Recent legislative proposals

- H.R. 4056, Science and Technology Regulatory Relief Act of 2012, proposed by Rep. Brian Bilbray (R-CA), would prevent states from duplicating FDA inspections of drug or medical device manufacturers.
- S. 2113, the Transforming the Regulatory Environment to Accelerate Access to Treatments Act, or Treat Act, proposed by Sen. Kay Hagen (D-NC), would speed new therapies for critical diseases through the FDA regulatory process.

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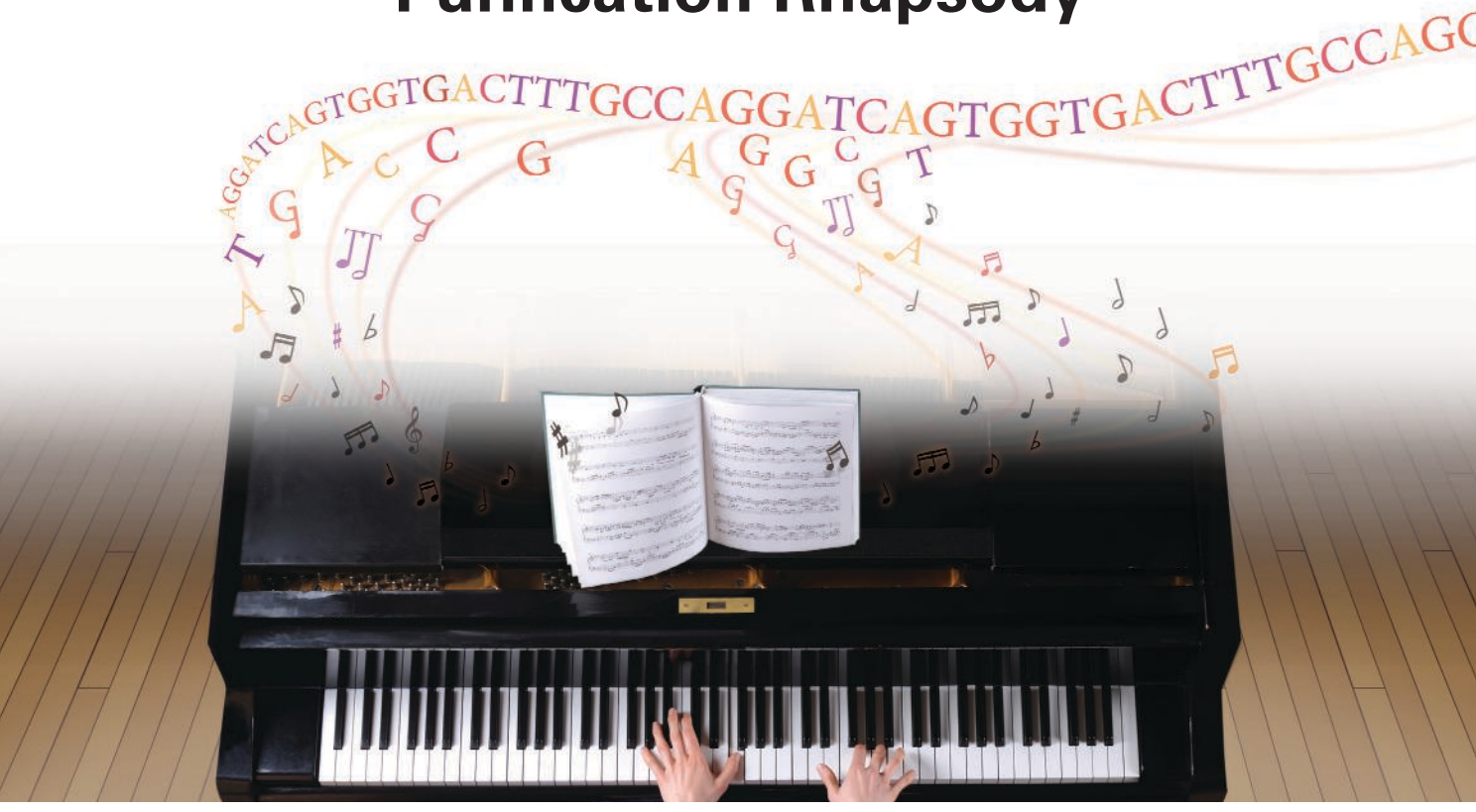

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Ways to Recover Lost Margins

Recovery audits and other best practices in procurement can improve the bottom line.

The past 15 years have witnessed extreme and mounting cost pressures on the pharmaceutical industry. This phenomenon has been driven by a host of changes, including:

- More costly and less productive R&D
- A saturated North American market where only a few new high-priced/high-margin drugs come to fruition
- Longer and more costly regulatory cycle times with greater drug-failure rates
- Advancing generic-drug competition and shorter patent life
- Outdated cost structures still laden with excess capacity and high-wage/high-benefit employees (although the industry has done much to change this through plant sales and layoffs).

Few can argue that the golden years of the pharmaceutical industry with high-margin products and regular new blockbusters coming into the market to replace products going off patent are over.

A CHANGING MODEL

Although there is sales growth in exciting new global markets, these markets simply cannot command the high-priced drugs of the past. Granted, the potential exists for significantly increased sales volume over time, but the increased sales will be at a lower price and at lower margins.

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To counter these trends, Big Pharma has aggressively deployed network rationalization strategies, other restructuring, outsourcing, and reorganizing, which have resulted in massive layoffs. Reducing infrastructure and operational costs has become the new norm within the industry. Some doomsayers are even predicting the demise of Big Pharma in the decades to come as there will no longer be a financial model that is attractive to investors. Now that may sound a bit farfetched, but one thing is certain: every function and every person is being called upon and challenged to become lean, to cut costs, and to do more with less.

> Every function and every person is being called upon and challenged to become lean, to cut costs, and to do more with less.

I've written many times in the past that adopting best-practice procurement methods is a great way to reduce costs and to recover margin. My experience has shown that when the right sourcing strategies are deployed and the maximum amount of spend is truly competitively bid, the resulting savings can range from 10–30% of the starting baseline pricing of a company's total third-party purchases. Additionally, if a company is willing to focus on specifications, requirements, demand, and consumption, especially when buying indirect goods and services, significant incremental savings can be achieved on an ongoing basis.

An example of the resulting margin improvement (i.e., recovery) from a best-practice procurement-transformation initiative is as follows. Take the case of a company that

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generates $20 billion in annual revenues and has total costs for third-party purchases (both direct materials and indirect goods and services) of $8 billion annually with gross margins of 33% (i.e., $6.67 billion). If a company reduced its costs by 10% (i.e., $800 million), its gross margin would increase to $7.47 billion, or a gross margin gain of 12%. If a company reduced the cost by 15%, the gross margin gain would be 18%.

Based on this example, it is clear that a transformed procurement organization is a strong investment. It also should be noted that when done properly, the transformation can be accomplished at net cost post initial investment. Some organizations are even lowering the overall cost of procurement through the use of innovative technology and outsourcing strategies and are seeing a sharp rise in procurement's return on investment.

RECOVERY AUDITS

With any improvement initiative, the secret to sustainability is to continue to improve and add new best practices as they become available. With that in mind, I offer some examples of what some organizations are beginning to do in this area, namely, recovery audits. Recovery audits are audits performed on past transactions to identify overpayments, recovering those overages, and putting safeguards in place to prevent recurrence. Recovery audits are becoming popular as a no-risk/low-risk method to recover overpayments associated with several areas in a company's business. The great thing about recovery audits are that there are many firms willing to perform the audit service and follow-up collections on a contingency fee basis (i.e., the firm will negotiate a split of the collected over payments). Recovery audits include payables audits, worker's compensation audits, telecommunications audits, and waste and recycling audits.

Payable audits. Payables audits are probably the most common recovery audit being performed today. Auditors look for items, such as duplicate payments, invoicing errors, wrong price paid, and other incorrect payments. Many firms have reported up to 2% overpayment on the sample data being audited. As monies are found, companies typically expand the scope of the audit.

Worker's compensation audits. The purpose of worker's compensation audits is to recover worker's compensation premium overcharges. Typically, the audit team will review the past five to seven years of insurance policies and premium calculations with the goal of finding errors and obtaining refunds. Various documents are reviewed, including final audit billing statements, experience-modification rating worksheet calculations, policy-declaration pages, auditor worksheets, loss-history summaries and claim reserves, and especially rating plans. Experience indicates that up to 70% of corporations will find that they have overpaid their carrier and will receive a refund as a result of this type of audit.

Telecommunications audits. Because the telecommunication industry has grown so complex and expensive, it is almost inevitable that waste and errors infiltrate the billing to an organization. The audit eliminates waste, corrects billing errors, and puts an organization in full control of future invoices. Auditors perform an in-depth analysis of local service, long-distance service, data lines and circuits, bandwidth usage, private lines, wireless service, teleconferencing services, equipment leases, and service contracts. Common issues that are addressed and corrected include hidden charges not on billing, overcharges versus contracted rates, incorrect long-distance carrier charges, duplicate charges, charges for unnecessary circuits, charges for services never ordered, and incorrect taxes and surcharges. History shows that corporations can lower their telecommunications bills by an average of 25% with the proper controls in place.

Waste and recycling audits. Independent specialists will perform free comprehensive waste audits that examines every aspect of a company's current waste and recycling services. These audits include contract compliance, thereby right-sizing a company's waste output to ensure that a company's out-density is within its industry standards, margin pricing, and cubic-yard evaluation. Most companies are overserviced and incur expensive bills for frequently scheduled hauler pickups. The specialists also will uncover potential revenues for a company from a more organized and aggressive recycling effort. Specialists are compensated with recovered monies on a negotiated basis or from helping to implement the necessary changes.

These are just a few examples. Recovery audits also are taking place for utilities, medical claims, merchant services (business-to-business transactions), sales and use tax recovery (for nonprofits), and property valuation, along with other areas where billing complexity exists.

Recovery audits are important tools for a company to benefit from improved practices and having additional funds returned and should be considered. ◆

Preparing for an FDA Inspection in a Global Pharmaceutical Environment

FDA inspections of foreign facilities are on the rise. The author provides a due-diligence checklist to prepare for such an occasion.

Foreign inspections have long been part of FDA's efforts in ensuring medical product safety and quality. In fact, FDA has been conducting foreign inspections for the past 50 years. It is through such foreign inspections that the agency monitors the manufacture of pharmaceutical products and ingredients that are imported into the United States. The primary goal of the inspections is to ensure that foreign establishments meet the same requirements as domestic establishments in regards to the quality, purity, potency, safety, and efficacy of pharmaceutical products marketed in the US. If a foreign pharmaceutical manufacturing establishment fails to meet FDA's cGMP standards—based on an inspection or otherwise—the agency has the legal authority to deny products manufactured at the violative facility entry into the US.

FDA officials acknowledge that the agency is far from achieving foreign drug inspection rates comparable to domestic inspection rates. Each year, however, FDA investigators are appearing more frequently at the doors of foreign manufacturing facilities. For example, between 2007 and 2009, FDA inspections at foreign pharmaceutical manufacturing establishments increased by 27%. The agency seems to have no intention of slowing down—FDA has created a dedicated cadre of foreign drug investigators and established permanent offices in Europe, China, India, Central and South America, South Africa, and the Middle East.

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The US government's increasing focus on foreign inspections should come as no surprise. Pharmaceutical manufacturing has become more global, and the US market has, in turn, become more reliant on foreign medical products. Based on FDA's estimation:

FDA has created a dedicated cadre of foreign drug investigators and established permanent offices worldwide.

- 40% of finished drugs, 80% of APIs, and 50% of all medical devices are currently imported.
- There was a 13% increase in pharmaceutical products imported into the US between 2002 and 2009.
- From 2000 to 2007, the importation of "high-risk" medical products, such as vaccines, quadrupled.
- In 2002, there were just over 500 FDA registered foreign drug-manufacturing establishments. That number grew to more than 3000 in 2007, and registered foreign establishments now outnumber registered US establishments.
- In 2000, the US imported roughly $1.7 billion more in biopharmaceutical and pharmaceutical products than it exported; by 2008, that gap grew to $18 billion.

Because of the dramatic increase in the volume of imported drug products and the increasing complexity of the global supply chain, FDA is operating as an internationally-focused consumer safety agency. In doing so, the agency is pressing forward with increased foreign inspections, as well as partnering with foreign counterparts to create global coalitions of regulators focused on ensuring and improving global product safety. A clear result

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of which has been the significant increase in Warning Letters and Untitled Letters issued for international drug quality issues—in 2005, three such letters were issued; in 2010, FDA issued 23.

As FDA's focus on foreign pharmaceutical manufacturing increases, it is critical that non-US facilities be prepared for an FDA inspection more than ever, particularly those establishments that have no—or limited—experience in dealing with FDA. Therefore, if your facility manufactures abroad for the US market, it is important to keep the following guiding principles in mind when preparing for an FDA inspection.

IMPLEMENT AN INSPECTION SOP

The first step in preparing for an FDA inspection is implementing an SOP that will govern employee activity during the inspection. This should be done whether or not an FDA inspection is anticipated. The SOP should provide guidance on a number of issues, including: greeting the FDA investigator, duties of key individuals, conducting tours of the facility, responding to FDA questions and requests for documents, employee documentation of the inspection, and inspection-closeout procedures.

When FDA schedules the inspection, obtain as much information as possible. FDA's foreign inspections are announced in advance, and are generally scheduled for a predetermined period of time. So when FDA schedules the inspection, obtain as much information from the agency as possible. The more that is known about a planned FDA inspection, the better. Specifically, determine the reason for the inspection (e.g., cGMP, preapproval, followup, or for-cause), when the inspection will start, how long the inspection will last, whom from FDA will be attending, and whether there are any special requests or documents to have ready. As soon as notification of the FDA inspection is received, alert the company's regulatory affairs, quality, and legal departments.

ESTABLISH AN INSPECTION TEAM

Once the dates of an FDA inspection have been established, make certain all crucial employees will be available during the inspection. Carefully select an inspection team that will be tasked with interacting with the FDA investigator. Part of this exercise is knowing who is crucial; knowing who is currently responsible and who was historically responsible; and ensuring that employees

understand their responsibilities. One of the worst things that can happen during an FDA inspection is having an unqualified or unprepared employee answering vital questions posed by the investigator.

REVIEW AGENCY GUIDANCE AND LEARN FROM OTHERS' MISTAKES

Prior to the inspection, review all the relevant and recent FDA Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER) guidance documents and compliance policy guides, as well as the International Conference on Harmonization (ICH) Quality Guidelines. These documents are key to understanding FDA's often-evolving view of industry standards, which is as important to comply with as FDA's specific cGMP regulations. Additionally, it is helpful to analyze past Warning Letters and available Form FDA 483s; these documents offer valuable insight into what FDA investigators are keying on during inspections and what issues investigators deem to be worthy of a Form FDA 483 observation.

ORGANIZE AND REVIEW DOCUMENTS

Ensure that all required documents are available for FDA inspection, and make sure they are organized, complete, and current. Reviewing key documents will allow employees to refresh their memory and understand the organization of documents. It is also advisable to have an English translation of critical SOPs and documents, if possible.

DISCUSS INTERNALLY ANY KNOWN DEFICIENCIES

Bring any known deficiencies to light; especially any that may relate to prior Form FDA 483 observations or recurring issues. The goal is to avoid any surprises during the inspection, as well as taking any preemptive steps to correct or mitigate the deficiency prior to the FDA inspection.

Employees should be instructed to ask for clarification if FDA's questions are not completely understood.

PLAN FOR ANSWERING INVESTIGATOR'S QUESTIONS

First and foremost, all employees need to be directed to be honest and to avoid any speculation. Of equal importance, be prepared to speak with one voice and avoid internal disagreements while in front of the FDA investigator at all costs. Also, employees should be instructed to ask for clarification if FDA's questions are not completely understood (e.g., be clear on what timeframe FDA's request for documents covers). This is important so that all questions and requests are fully addressed, while at the same time refraining from saying more than what is necessary. Employees should also understand that it is acceptable to take a reasonable amount of time in responding to the investigator's questions and requests; responses do not always have to be instantaneous.

CONDUCT A MOCK INSPECTION

Generally, the best way to prepare for an FDA inspection is to actually practice one. This can help pinpoint any weaknesses in procedures or inadequacies in records, and it prepares employees for the types of questions that will be asked by the FDA investigator. Another benefit of practicing an inspection is—by providing a dry run for employees—they will be more comfortable when the actual FDA inspection occurs. The mock inspection should be scheduled far enough in advance to afford time to implement any corrective actions which become needed as a result of the mock inspection.

HAVE A ROOM RESERVED FOR THE INVESTIGATOR

While a simple matter, always set aside a quiet and securable conference room or office for the FDA investigator to review documents and to conduct his or her business. Ideally, this room should be away from any high-traffic employee areas, as well as the manufacturing areas.

An FDA inspection is an important event and should not be taken lightly. This is particularly true for non-US facilities that manufacture biopharmaceuticals, pharmaceuticals, and APIs for US importation. In these cases, the legal standard for FDA to refuse the entry of drug products into the US is significantly lower than what is required for FDA to initiate a domestic enforcement action (i.e., a seizure or injunction). FDA can refuse admission of an imported drug product if the product merely appears to be violative.

One way a drug product can appear to be violative—and therefore be denied entry into the US—is if it was manufactured at a foreign establishment that had a poor FDA cGMP inspection. Therefore, taking the time to carefully prepare the items discussed above, in advance, can greatly reduce any tension and increase the likelihood of a positive FDA inspection. ◆

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A Strong Start to 2012

Better news about the global economy buoys life-sciences funding.

The strong boost to biotech stocks in the first two months of the year has energized the sector and allowed companies to make deals and raise funding. Of the 340 life sciences companies trading at or above $1 at the end of 2011, 253, or 74.4% of them, are trading higher after the first two months of the year, while 25% of those companies are up more than 25% so far this year.

There has been a sharp improvement in the price of life-sciences stocks as economic news in the US has been generally positive this year, actions in Europe to address the debt crisis advance, and news within the sector is encouraging. All of the Burrill Life Sciences Indices have posted gains for the year with the flagship Burrill Select Index the strongest performer, climbing 15.5% through the end of February. The Dow Jones Industrial Average, up 6% for the same period, closed above the 13,000 mark in February, the first time since 2008.

We are still in an environment where markets can turn quickly in response to negative news. Smart companies will take advantage of opportunities to secure financing and get deals done. Life-sciences companies through secondary offerings raised $1.4 billion in the first two months of 2012 through 29 financings, 23 of which were completed by therapeutics companies.

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Roche's hostile $5.7-billion bid for the tools and sequencing systems company Illumina reflected strong dealmaking activity for the life sciences at the start of the year. The wrangling between Roche and Illumina is likely to go on for months. The deal reflects Roche's efforts to build itself into a personalized medicine powerhouse and its belief that sequencing technology will eventually migrate from the laboratory to the doctor's office.

Smart companies will take advantage of opportunities to secure financing and get deals done.

Some of the year's biggest acquisitions have been traditionally structured takeovers. Bristol-Myers Squibb agreed to acquire hepatitis C drug developer Inhibitex for $2.5 billion. Amgen said it would buy Micromet, which is developing a new class of drugs that enlist the body's T-cells to battle cancer, for $1.2 billion. But a number of transactions of privately held companies included large milestone payments.

Privately held companies that are being acquired today often find they will have to wait to reap the rewards of a transaction. In the absence of a vibrant initial public offering (IPO) market, buyers have the upper hand and often insist on sharing risk. Increasingly, the structure of these agreements may borrow from those of partnerships and may mean investors seeking exits will have to be patient to realize their full return.

Celgene agreed to acquire privately held Avila Therapeutics for $350 million plus milestones that could push the total value of the deal up to $925 million. Dainippon Sumitomo said it would acquire privately held Boston Biomedical, a developer of oral

therapies that target cancer stem cells with its lead candidate in late-stage clinical testing, for $200 million in upfront cash and milestones that could push the total deal value to $2.6 billion. Biogen Idec said it would acquire privately held Stromedix, a developer of therapies for fibrosis and organ failure with its lead candidate in mid-stage clinical testing, for $75 million upfront and milestones that could push the total deal value to $562.5 million.

A total of six companies completed IPOs on US exchanges in the first two months of 2012, but investors still lack enthusiasm for new issues in the sector. Five of the six issues came below their target price range. Only Verastem, a preclinical therapeutics company developing drugs that target cancer stem cells, managed to price at the midpoint of its $9 to $11 target, raising a total of $55 million by selling shares at $10 each. Existing investors committed to purchasing nearly a third of the offering. The company is led by Christopher Westphal, the former CEO of Sirtris Pharmaceuticals, which he sold to GSK in 2008 for $720 million.

Renewable Energy Group raised $72 million in the first life-sciences IPO of the year. The biodiesel producer sold 7.2 million shares at $10 each, well below its range of $13 to $15 a share. The therapeutics companies Cempra Pharmaceuticals and ChemoCentryx, the digital health company Greenway Medical Technologies, and the agbiotech Ceres all went public in February. Collectively, these companies that went public in the first two months of the year hoped to raise as much as $505.7 million, but raised $354.4 million, nearly 30% less than they sought. They also needed to sell 10% more shares than they set out to sell in order to raise what they did.

Venture financings also got off to a strong start with companies raising $1.8 billion globally in January and February, a 22% increase compared with the same period a year ago. Among the largest financings so far was startup Warp Drive Bio's potential $125 million in funding, $75 million of which is equity financing tied to the achievement of milestones. The company, backed by Third Rock Ventures and the drug giant Sanofi, is using proprietary genomic tools to search inside microbes for potential new natural product drugs. The deal comes with a built-in exit for investors, by requiring Sanofi to buy Warp Drive should it meet its milestones.

On the regulatory front, the Obama Administration's proposed budget for FDA in fiscal year 2013 calls for $4.5 billion, a 17% increase in funding. The increase is expected to come almost entirely from industry user fees. User fees overall are expected to fund about 45% of the agency's budget. The government's contribution to funding FDA will essentially remain flat under the proposal.

It is critical that Congress move quickly to pass the renewal of the Prescription Drug User Fee Act (PDUFA) and not allow the legislation to get bogged down in extraneous issues. User fees provide nearly two-thirds of the funding for drug reviews today. They do not, however, address the chronic underfunding of the agency, which Congress will also need to address at this time when there is continued pressure to cut spending. ◆

25th Anniversary
BioPharm INTERNATIONAL
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Retrospective

A 25-Year Retrospective on GMP Training: Then and Now

Throughout *BioPharm International*'s 25th anniversary year, we will be looking back at articles published in the first volume of the journal. This month, we rewind to an article titled "Good Manufacturing Practices Training" (1). Here, the original article's author, Carolyn M. Orelli, Manager, Quality Assurance, Bayer HealthCare Pharmaceuticals, provides an update to GMP training and how far it has come.

In the past 25 years, there have been many changes in GMP Training. These changes were not in the GMP training concepts themselves, but in the "c" in cGMP. It is the practical applications of training that have changed over the years. Some changes were subtle; some were more drastic (and even dramatic). But all can be summarized in three words: technology, technology, technology.

My 1988 article talked about GMP regulations, a commitment by upper management, and the need for qualified trainers. These basic requirements haven't changed. However, the use and sophistication of computers have provided opportunities to change program design, training documentation and training styles.

PROGRAM DESIGN

In 1988, training was comprised of a combination of reading SOPs (by the binder-full), hands-on demonstration (otherwise known as "passing on the tribal knowledge") for on-the-job training (OJT), and seminar-style presentations (usually for the much anticipated annual review of GMP concepts). Today, employees are still required to read the applicable SOPs, although the training curricula is now commonly managed with computer software, allowing the SOP listing to be specifically targeted and customized for individual jobs, job assignments, and for the degree of involvement and responsibility (e.g., "read and understood" versus interactive module). Operators are still required to learn and demonstrate competence with job-related techniques, whether that means assembling equipment, running an assay for quality control, or reviewing documentation for quality assurance.

Training concepts and training departments have become more sophisticated and knowledgeable.

But today, in 2012, another form of training is frequently used for both on-the-job and GMP regulations training: computer based training (CBT), or training using a "wiki" database. Essentially, a file is prepared with training materials, either within the pharmaceutical company, adapted by an outside vendor, or purchased off the shelf. Employees review the training materials online and then answer questions embedded in the file to demonstrate competency with the material.

TRAINING DOCUMENTATION

In 1988, all training was documented, but typically based on a paper system, such as an attendee sign in sheet, or a trainer/training record sheet. This sheet was duplicated and filed in one or more folders, as applicable. Retrieving the specific page, for a performance review by a supervisor, or


Good Manufacturing Practices Training

View "Good Manufacturing Practices Training" by Carolyn M. Orelli at BioPharmInternational.com/Retrospectives.

at the request of an auditor or regulatory agency, was frequently a challenge. But with the introduction of Learning Management Systems (LMS) software, training documentation has also reached the computer age of data storage, with the power to retrieve as needed. In fact, some biopharmaceutical companies are using the second or even third generation of validated LMS software.

LEARNING STYLES

In 1988, most training programs, including GMP programs, were in their infancy and frequently used a one-size-fits-all approach. Some trainers tailored their approaches by targeting the audience, usually by department. For example, GMP training for R&D personnel might include scientific reasons behind the regulations, while training for maintenance personnel might include a "what's in it for our operations as long as we are required to comply with the regulations" approach. Over the years, training concepts and training departments have become more sophisticated and knowledgeable, including awareness of differences in learning styles (i.e., visual, auditory, and kinesthetic) when designing training materials. Now, an experienced trainer expects to include aspects of all three learning styles, and also address the learning preferences of all ages of employees (e.g., Millennium, GenXer, Boomer). This is an added requirement for training design, but facilitates comprehension of the material.

SUMMARY

cGMP learning has changed in 25 years. Is it more challenging for the trainer? Yes, but it's also become more interesting for both the trainer and the trainee. Is the training program more sophisticated? Yes. Is the training program more comprehensive? Usually. Is the documentation more readily retrievable? Yes. Do all these differences make GMP training more effective, and more current? Certainly.

REFERENCE

1. C.M. Orelli, "Good Manufacturing Practices Training," *BioPharm International* **1** (4), 38–40 (1988). ◆

Optimizing Adjuvant Filtration

A technical roundtable

Adjuvants are becoming more common in vaccine and other drug formulations to increase therapeutic response. Some of these substances, however, are close enough in size to bacteria that they are unable to pass through sterilizing-grade filters. Others have low surface tension that can reduce a filter's bacterial retention. As a result, adjuvants can cause premature plugging of filter membranes and reduce filter capacity. BioPharm International spoke to several industry experts to gain insight on resolving these technical challenges.

PHOTO CREDIT: SARTORIUS STEDIM

Featured in the roundtable:
Holger Bromm, director of marketing and product management filtration technologies at Sartorius Stedim Biotech; **Jerold Martin,** senior vice-president of Global Scientific Affairs at Pall Life Sciences; **Peter Koklitis,** a technical filtration specialist at 3M Purification in the United Kingdom; and **Jim Powell,** business development manager of Asahi Kasei Bioprocess.

REDUCING BLOCKAGE

BioPharm: Novel adjuvants are often based on emulsions or liposomes, which are suspensions of small particles made up of surfactant or lipid particles. Because these formulations have a relatively high viscosity and because the typical particle size of the micelles or liposomes is close to the size of the smallest bacteria to retain, they result in a difficult separation process. In addition, these fluid streams often contain high particle loads which can cause premature plugging of sterilizing-grade filters. How can pharmaceutical or filter manufacturers reduce such filter plugging or pore blockage?

Bromm (Sartorius Stedim): One possibility for filter manufactures to deal with these challenges is to develop sterilizing-grade filters that specifically address these needs. According to our experience at Sartorius Stedim, highly asymmetric membranes, such as polyethersulfone (PES) membranes provide higher flow rate and capacity for such type of formulations compared with symmetric membranes. According to practical experiences, the use of a heterogeneous double-layer membrane construction provides total throughput advantages compared with single layer membrane filters. The prefilter (i.e., upstream layer) protects the final membrane (i.e., downstream layer) from premature plugging. Of high importance is to find the optimal graduation between two membranes. Studies with model solutions and test results with actual formulations in field tests have demonstrated that the combination of a finer prefilter membrane

Protein Purification Using Single-Use Technology

Key experts delve into specific challenges in protein purification. Below are responses from Mark A. Snyder, PhD, manager of the Applications R&D Group, Process Chromatography Division, at Bio-Rad Laboratories; and Uwe Gottschalk, vice-president of purification technologies, Sartorius Stedim Biotech.

BioPharm: What are the challenges to developing a reliable, robust means of performing protein purification in a single-use unit? What properties would a single-use product for protein purification need to be economically viable?

Snyder (Bio-Rad): The challenges are two-fold: economic and technological. For single-use to be economically viable, the cost of the purification matrix must be significantly lower than it is today. Keep in mind that the only parts of the process that single-use avoids are the price of water used in the cleaning and storage steps, the one-time cost of cleaning validation, and the one-time costs of tankage. Contrast this usage with the ongoing, every-time expenses of the disposable module and the economics are rarely there. The current disposable market today is largely geared towards pilot-scale columns. The technology hasn't progressed to a state where such modules can be easily fabricated and packed when the size of the column is, say, one meter, for several reasons:

- Weight: a prepacked column of 100 cm ID x 20 cm H will lead to a weight around 200 kg and cannot be handled manually.
- Transport and packing: rigid chromatography media require special packing skills (vibration) to guarantee a fully consolidated and therefore stable resin bed.
- Infrastructure (i.e., packing equipment) and knowledgeable personnel for the packing of such big columns is weak.
- Hardware and supply chain: manufacturing of the column parts of the dimension mentioned above requires a specialized supplier.

Additional issues (e.g., inadvertently getting air into a column during the equilibration phase) cannot be effectively dealt with in a disposable. A reusable column requires repacking; a disposable column would have to be thrown out and replaced with a new, air-free column.

Gottschalk (Sartorius): Industry is changing to a 'market-pull' scenario, mainly due to regulatory pressure to pro-actively provide best practice. Single-use manufacturing adds value in certain downstream unit operations. While such practice has never been questioned for steps such as virus or sterile filtration, we are in the middle of that shift in chromatography and X-Flow filtration. Although it can be demonstrated that single-use strategies provide better process economies, their main advantages stem from factors such as accelerated development timelines and risk mitigation.

BioPharm: What recent developments in membrane adsorbers could lead to single-use technology for protein purification? Could membrane adsorbers replace packed-bed column chromatography?

Gottschalk (Sartorius): Membrane adsorbers offer two main advantages compared to packed-bed chromatography: the fluid dynamics of a convective media that can process large feed-stream volumes with extremely high flow rates, and large pore sizes that provide accessability and thus high dynamic binding capacities for large molecules such as DNA and viruses.

As a result, single-use membrane chromatography devices are typically much smaller in size and require only about 5% of the original buffer volume. The sweet spot for membrane chromatography is related to these two stand-alone features and it shines in areas like contaminant removal (polishing in flow-through mode) and purification of viral vaccines. In these applications they start dominating the industry's development platforms and will take over from resins completely. Recent developments include salt-tolerant chemistries on membranes that bind viruses under physiological conditions (no in-process dilution requirements).

BioPharm: What technologies in development could make protein chromatography a continuous process?

Gottschalk (Sartorius): In general, continuous processing offers the advantage of higher productivities, from a smaller footprint to an advantageous process economy and chromatography. Technologies such as simulated moving-bed chromatography have the potential to decrease column sizes because they use the total binding capacity as well as the overall lifetime of the chromatography medium. In this setup, a single-use design is possible if, for example, the same sample of medium is recycled within the purification of just one batch of product. Although this scenario would cut costs during clinical manufacturing, it is probably less beneficial in routine manufacturing and questions of scale up remain.

with the final 0.2 µm membrane achieves better results compared with combinations with a coarser prefilter membrane for adjuvants applications.

Pharmaceutical manufacturers should carry out filtration studies to compare the performance of different membrane materials and construction principals of filters to find out the optimal solution for their specific formulation. Furthermore, the use of prefilters should be considered in such studies to protect final sterilizing-grade filters effectively and to reduce costs and filtration time. These studies can be used to determine the optimal parameters for the filtration process, such as differential pressure or temperature. Increasing the temperature can enhance filterability depending on the stability of the solution at higher temperatures. The same filter-selection process may be applied for other protein therapeutics or vaccines.

Martin (Pall): Pharmaceutical manufacturers can reduce filter plugging by optimizing formulation and process conditions for desired filter life, along with selection of appropriate filters with suitable capacity. Filter manufacturers can provide technical support for this process by conducting feasibility (filterability) trials, selecting appropriate filter-media grades, sizing of filter cartridges or capsules, as well as ultimately applying that knowledge to the development of new filters capable of providing greater capacity.

Process parameters such as pressure, temperature, and flux (i.e., flow per unit area) can have a large impact on filter throughput and capacity. For example, with complex plugging biological fluids, performing the filtration in a constant flow mode, increasing pressure differential to maintain flux rather than operating under a constant pressure mode can often have a positive impact on filtration throughput (capacity). Process temperature can also have an impact but is product-dependent and needs feasibility (filterability) tests to determine whether an improvement can be achieved through modification. Optimizing these performance variables is an acceptable (and recommended) technique to reduce the risk of premature blockage for vaccines or protein therapeutics.

Koklitis (3M): The plugging of membrane filter systems by adjuvants is particularly undesirable when the process step has been validated to provide sterility assurance. The risk of filter plugging can be reduced by careful control of the filtration operating conditions, such as inlet pressure and optimum flux. The lifetime of the sterilizing-grade filter membrane will be greatly determined by the particle load in the process feedstream and the capacity may be extended with a prefiltration stage. A prefilter rated at 0.45 µm will remove larger emulsion micelles or liposomes which might ordinarily plug a sterilizing 0.2 µm membrane. Another option is to consider a 0.2 µm-rated bioburden reduction membrane as a prefilter. This can be of the same material as the final sterilizing membrane to simplify validation and may be effective for removing larger particle sizes from the process stream as a result of its pore size distribution. The prefiltration system selected should be sized appropriately to meet the demands of the process stream to minimize the expense associated with the final sterilizing membrane stage. When emulsions are used, the pharmaceutical manufacturer could investigate an adjuvant formulation with a sufficiently small particle size to make it filter-sterilizable.

Some studies with oil-in-water emulsions have shown that increasing the pressure drop across the membrane can increase filter capacity. The coating of bacteria on the membrane with emulsion has been considered to contribute to bacterial penetration. In such instances, higher bacterial retention may be achieved by increasing the temperature if cold conditions are currently used. However, the reasons for adopting cold filtration (e.g., to maintain protein stability) may present an obstacle to implementing a change.

Powell (Asahi): This is rather hard to answer because the blocking can occur due to a wide range of issues related to product use and conditions such as pH, conductivity, protein concentration, viscosity, temperature, membrane incompatibility with what is in the adjuvant, and so forth. The best solution would be to better characterize the adjuvant, the product, and the combination to find the most stable and best filter condition possible, where material is not precipitating, too viscous, too high a concentration, and/or at the early stage or "edge" of aggregation and the filter type where the adjuvant's oil, if present, does not bind to or change/damage the membrane itself.

There are really two choices: the brute force method, where one throws more membrane at the problem, or the better method, which would be to choose the right adjuvant for the job and choose conditions that fit into a high stability window of operation for the API. Another more sophisticated solution to these kinds of clogging problems is to use a cascade of filters that end in the final desired porosity. The upstream filter(s) can act as prefilters to increase final filter capacity.

LOW SURFACE TENSION

BioPharm: Low surface tension of some adjuvant solutions can reduce the efficiency of filters' bacterial retention. How can this problem be mitigated?

Bromm (Sartorius Stedim): It is advisable and required by regulators to carry out a comprehensive filter validation study, including bacteria-retention testing, simulating worst-case process parameters with actual product formulation using process related (i.e., pleated) scale-

down filter devices. The design of the filtration system should consider reducing filtration time and differential pressure because these two parameters, among others, may increase the risk for bacterial breakthrough. During a filter evaluation study, the impact of different inlet pressure filtration conditions should be assessed, including constant flow or constant pressure conditions. Constant flow conditions may increase the risk of bacterial breakthrough, because of the increased differential pressure required to keep the flow constant during the filtration process and increased filter blocking.

The use of filters specifically designed for adjuvant filtration as explained above is highly recommended because those filters will keep the process parameters at a moderate level. It is recommended to carry out a bacterial-retention study early in the filter-selection process to find the optimal solution based on retention efficiency and highest filtration capacity.

Martin (Pall): Statistical and empirical studies at Pall Corporation have identified low surface tension of some adjuvant solutions as a risk factor for reduced bacterial retention efficiency of most sterilizing grade 0.2 μm rated membrane filters. The mechanism by which bacterial retention is reduced under lower surface tension in these fluids is not yet fully elucidated. Some mitigating factors appear to be membrane structure and layering of multilayer media, operating conditions, as well as reduction of bacterial bioburden or challenge levels and reducing challenge duration. Fluid surface tension affects the interactions between the bacteria and the membrane flowpath surfaces, but detailed mechanisms are not well known and specific surface tension thresholds cannot be determined.

Membrane surface chemistry is also an element that may mitigate the negative impact of fluid surface tension. Determining how and to what extent membrane-surface chemistry can enhance retention requires extensive studies. Filters with positive zeta potential, which provide enhanced adsorptive removal properties for bacteria in aqueous ionic solutions, have been used in the past for such purposes. This was also one of the capability advantages of asbestos-containing filters, although these are no longer used because of asbestos safety concerns.

Koklitis (3M): Such reduced filter efficiency can be related to the mechanisms involved in bacterial retention, which can be based not only on sieving but also on entrapment and electrostatic attraction. The adsorption of bacteria to the membrane polymer surface can be caused by any combination of forces, including hydrogen bonding, charge-induced, and Van der Waals interactions. The presence of liposomes, oils, or surfactants in a process stream can disrupt these adsorptive interactions and consequently reduce retention of bacteria within the membrane structure.

When there may be a high risk of bacterial penetration, it should be identified and considered in the planning of a filter validation study. The required minimum bacteria challenge (1×10^7 colony forming units of *Brevundimonas* diminuta per cm^2 effective filter area) must apply, although an upper challenge level can be considered and restricted to one log higher. In a full-scale production process, the bacterial challenge to the final filter membrane may be controlled by introducing a prefiltration stage that has been demonstrated to be effective for bioburden reduction. The careful management and control of the operating conditions during process filtration will also help mitigate the risk of bacterial penetration, with attention to flow rate and filter area sizing to avoid high pressure drop.

Powell (Asahi): This issue is typically not applicable to Asahi products, but with some filters, the lower surface tension can change the effective porosity rating of the membrane, allowing larger particles to slip through the membrane's holes. These low viscosity adjuvants effect the thickness of the boundary layer (where flow velocities at the membrane surface are at or close to zero) which, in turn, alters the effective pore size under those conditions. It can also affect how the API and contaminants build up around the membrane's pores hence altering the effective pore size. One can screen different membrane types, porosities, and brands of filters, and work closely with the membrane filter supplier to choose the best filter for the application.

ADJUVANT TYPE

BioPharm: Can certain types of adjuvants cause fewer problems with regard to filters' bacterial retention?

Bromm (Sartorius Stedim): A review of validation studies and field tests for a broader variety of fluid formulations indicates that low surface tension formulations, such as many adjuvants or adjuvanted vaccines, present a higher risk for bacterial penetration of sterilizing-grade membrane filters. Among such formulations, according to the data analyzed, liposome formulations present a higher risk than surfactant containing solutions. Therefore, the use of such formulations may be a suitable alternative to replace more critical formulations where applicable.

Martin (Pall): It is possible that certain adjuvants and related low surface tension fluids may be intrinsically less likely than others to cause reduced retention efficiency by membrane filters. However, there is insufficient data at this time to draw firm conclusions and make recommendations. In addition, awareness among vaccine producers that selection of

surfactant-containing adjuvants and processing conditions can influence bacterial retention efficiency of sterilizing filters is not yet widespread. Until then, filter manufacturers must continue to work with vaccine developers to define appropriate membranes and optimize reasonable processing conditions to sterilize any vaccine formulation. Certainly, elaboration of an optimum adjuvant with such a goal would require an extensive amount of work and a very close partnership between filter manufacturers and vaccine producers.

Koklitis (3M): The choice of adjuvant is dependent on meeting the requirements of the process under consideration. The pros and cons of using a particular type of adjuvant must be considered and compared. When liposomes are selected as adjuvants their role as antigen carriers is utilized along with their immunological enhancement effect.

Powell (Asahi): These issues should be discussed with the membrane supplier's technical support teams and if they can't help, the filters must be screened to choose the best solution for the filter application. The answer depends on the membrane chemistry, but for large porosity filters, surfactant-containing solutions are typically not that large of a problem. Smaller porosity filters can be dramatically impacted in a negative way.

FLOW MAINTENANCE

BioPharm: How can manufacturers maintain product flow g during adjuvant filtration?

Bromm (Sartorius Stedim): For the manufacturer of the adjuvants, it is important to study and understand the process variables involved in making the adjuvant. The process variables identified to have a significant impact on the filterability of the formulation should be controlled carefully and kept within a narrow operating window. This will enable constant performance of the filtration process within established process parameters.

Martin (Pall): Filter plugging may or may not be an inherent part of a filtration process, depending on the particulate nature of the influent solution. An efficient filter is designed to retain bacteria and therefore tends to retain any particulate of a similar and larger size (e.g., micelles, liposomes). The ideal filter, with an extremely narrow pore-size distribution, a very high porosity, free of pinholes or other defects, and with sufficient area, will present the best compromise between bacterial retention and filtration capacity.

If a specific flow rate is desired over the duration of a filtration operation where the potential for plugging exists, the filtration operation should be performed under constant flow mode using an appropriately sized filtration area. Product flow can be maintained by increasing the inlet pressure as needed. Throughput of complex biological fluids often benefits from operation in his constant flow mode, as opposed to operating at high initial pressure and allowing flux to decay as the filter plugs.

With adjuvanated vaccines, or similar products at risk for reduced bacterial retention efficiency, preliminary filterability trial performed at the initial stages of process developments can identify filters providing the highest level of sterility assurance for further formulation or process optimization, perhaps including limited microbial challenges to confirm initial suitability. Further filterability studies can then focus on optimizing process time and economy under operating parameters known to further increase bacterial retention likelihood with these highest assurance filters. This will maximize both retention and throughput to provide for successful sterilizing filtration, validation, and processing.

Koklitis (3M): As mentioned, the careful management and control of the operating conditions during process filtration is usually advantageous for achieving consistency and robustness. In addition, the choice of filter membrane type can can contribute to maintaining a consistent flow. An asymmetric membrane structure, with a more open upstream zone, can provide a relatively higher initial flux, for example, which results in higher filter capacity for some process streams.

A higher filter surface area can be obtained per cartridge cylinder by selecting products that use advanced pleat technologies, thus enabling higher throughput without increasing filter-system size. This approach may help with filtering highly viscous process streams, such as emulsions.

Powell (Asahi): Large areas of membrane is the brainless solution, but working with filter vendors and doing DOE-based filter screening under the desired, "high stability" API conditions is the better choice.

Just like in horse racing, where some horses perform better than others on different courses, choosing the right filter type or perhaps a cascade of filters can solve the problem and provide a balanced solution to your filtration problem. If your feed contaminant is primarily a slowly precipitating molecule of some sort, a relatively small coarse filter such as a 1 μm or 5 μm might be able to trap it and allow a medium-sized sterile grade filter handle the higher flow rate and process larger volumes.

Depth filters often provide significantly higher capacity than membrane filters so placing them upstream of a sterile grade filter is often a good idea when possible. As with any filter, but especially depth filters, a study of undesired reduction (by binding) in solution components should be considered. Find a balanced approach to this cascade of filters, with each filter sized appropriately to deal with and control the specific contaminant that causes the processing roadblock. ◆

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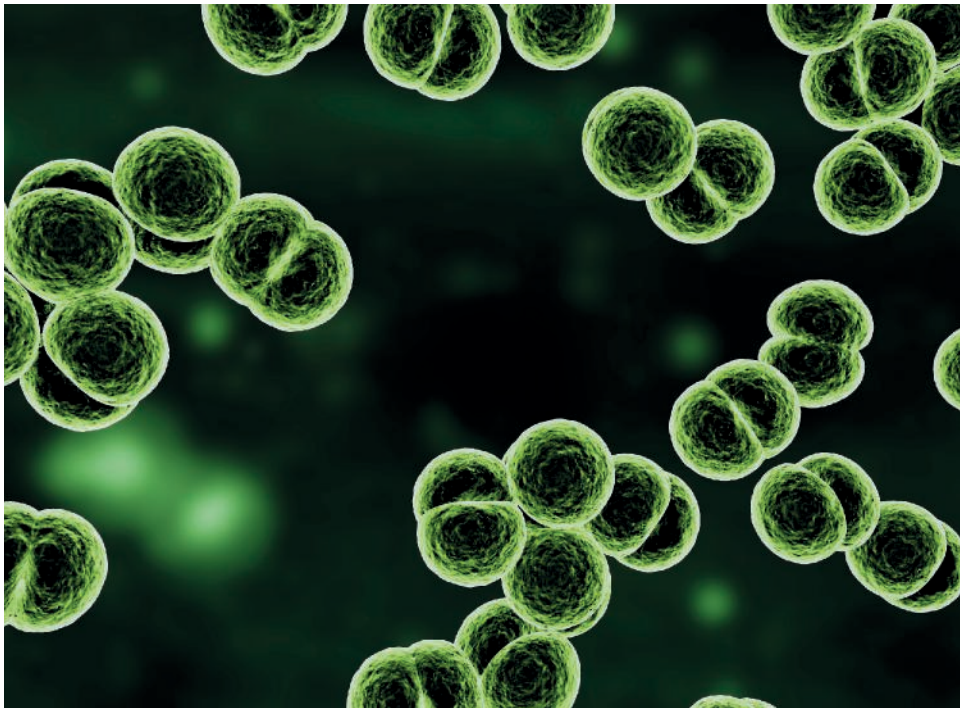

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The authors describe a new assembly for bulk and final drug product filling operations.

Increased regulatory expectations and the need to mitigate risk have popularized the use of redundant filtration for bulk and final fill operations. Single-use redundant filtration (SURF) assemblies are an efficient and flexible alternative to stainless steel systems because they eliminate clean-in-place (CIP), sterilization steps and the associated validation protocols. Preparation time can also be significantly reduced when using single-use assemblies because of their presterilized format and the ease with which they can be handled. Redundant filtration operations in multiproduct facilities can be performed without spending the extra validation time that is often required for non-disposable systems.

This article identifies a suitable design for redundant filtration operations using single-use technology and standardized assembly components. The design was finalized with input from a global technical and quality team with consideration given to international regulatory requirements. The article also demonstrates the capability of the assembly to withstand the high pressure that is used for integrity testing and drying. Pre-use integrity testing was performed on both filters. Using hydrophilic/hydrophobic filters on the assembly outlet eliminated flush volume limitations caused by catch bag size. Assembly specifications, such as leachables and extractables, hold up volume and flushing requirements, were established for a single-use assembly.

MEETING REGULATORY EXPECTATIONS

As defined in PDA Technical Report 26, redundant filtration is a "type of

Ranjeet Patil, is a process engineer II; **Michael Felo, is an** applications engineer consultant; and **George Oulundsen, is a** process engineer III, all at EMD Millipore.

serial filtration in which a second sterilizing-grade filter is used as a backup in the event of an integrity failure of the primary sterilizing filter." The pore size of the sterilizing-grade filters may be the same or tighter than the primary filter (1). Other regulatory bodies (e.g., FDA, EMA and SFDA) have also issued their own guidelines for sterile filtration. According to FDA's aseptic processing guidelines published in 2004, it is recommended that redundant filtration should be considered in many cases where liquid is sterilized by filtration (2). EMA's 2008 GMP guidelines state that because of potential risks of sterilization by filtration, a second filtration step as close to the filling point as possible is advisable (3).

Designing a redundant filtration system that meets regulations and recommendations is challenging. For stainless steel systems, EMA recommends that integrity testing should be performed on sterile filters before use. To do this, filters must be fully wetted without breaching the sterility on the downstream side of the assembly. Many conventional stainless steel facilities employ a "catch can" with a sterile vent filter to collect the initial flush liquid from the wetting step. Prior to use, additional time is required to sterilize, maintain and store the catch can. In addition, use of a catch can constrains the total flush volume that can be used if the filters need to be rewetted (e.g., in a repeated filter integrity test).

Disposable or single-use redundant filtration (SURF) assemblies offer a flexible solution for this relatively complex operation (4). These assemblies can be pre-sterilized by the supplier using gamma irradiation and there is no need for cleaning after use because assemblies are self-contained and entirely disposable.

PROPOSED SINGLE-USE PROCESS SOLUTION: DESIGN CONSIDERATIONS

Many biopharmaceutical companies already use variations of SURF assemblies for final and bulk fill operations. However, preparation and utilization sequences may differ across processes and geographies because of differing national guidelines.

Figure 1: Utilization sequence options for single-use redundant filtration assemblies. F1 is the first liquid filter. F2 is the second liquid filter.

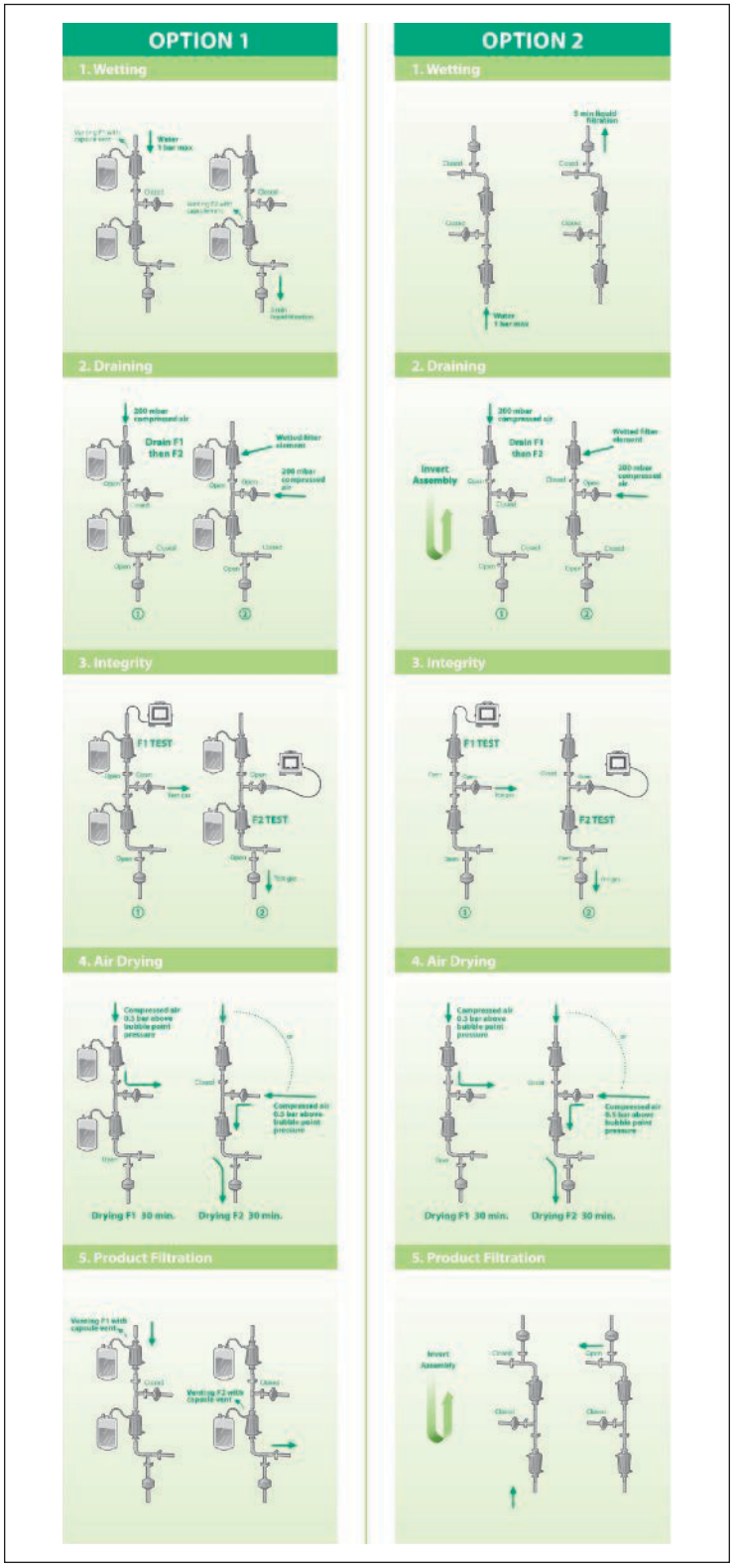
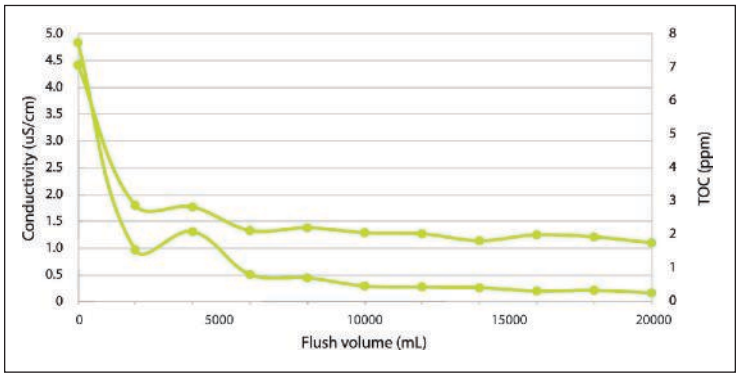


Figure 2: Total organic carbon (TOC) and conductivity (µS/cm) versus flush volume (mL).



This study reviewed different redundant filtration assembly designs and operating sequences, and proposes a new SURF assembly that has greater operational robustness and minimizes the risk of product contamination. Below are the major design considerations for the assembly (see Figure 1):

- A barrier filter (0.2 µm, EMD Millipore) was included in the design as a combined liquid and gas outlet. The barrier filter contains both hydrophilic and hydrophobic sterilizing-grade PVDF membrane, which can exhaust both air and water from the assembly. As a result, it can be used as the initial filter flush outlet and as a sterile air outlet during integrity testing and the filter drying step. Such a filter further solves the problem of flush volume constraints imposed by the catch bag/tank size. The assembly can be wetted and tested for integrity multiple times without breaching the sterile envelope.
- Catch bags were attached to the vents of the liquid filters to collect liquid during venting.
- Gamma stable vent filters were attached to the bags to enable passage of air during venting.
- A hydrophobic PVDF filter was added on the air inlet line to ensure sterility of the air coming into the assembly for integrity testing.
- Single-use sterile connectors were used at the assembly's inlet and outlet to assure sterile connections during operation.
- In-line liquid filter capsules were selected (as opposed to T-line capsules) to reduce the hold-up volume.
- The assembly was used in the vertical orientation to achieve better draining after wetting and during product recovery after filtration.

The catch bag on the first liquid filter is primarily in place to avoid the liquid spill that can occur during venting for water flush and product filtration. With some minor modifications, the catch bags on both the first and second liquid filters can also be used for in-process sampling. The catch bag on first liquid filter and the separate air inlet line (with an air filter near the feed inlet) are additional features that are incorporated to ensure cleanliness and ease of operation.

Pre-use, post-sterilization integrity testing of a redundant filtration setup can be challenging. With either stainless steel or a single-use assembly, it is critical to maintain setup sterility during every step. The efficiency of the filter wetting step is also important to avoid false negative integrity test results. For high-value products, the drying step after integrity testing is crucial to minimize product dilution. Figure 1 outlines the utilization sequence for SURF assembly before use. Along with the points mentioned above, operator convenience and regulatory compliance were also considered.

A flushing test was conducted to record the reduction of total organic carbon (TOC) and conductivity with flush volume. The filters and assembly were flushed with deionized (DI) water at a flow rate of 250 mL/min for a total of 20 L. The assembly effluent was sampled at 1 L intervals and tested for conductivity and TOC. Analytical results for flush filtrate samples are summarized in Figure 2. At the end of 20 L reverse osmosis (RO)/DI water flush, TOC and conductivity were 0.231 ppm and1.1 µS/cm, respectively.

COST ANALYSIS

Traditionally, the comparison of single-use versus stainless-steel processes is made on the basis of consumable cost versus capital cost, but other costs must also be taken into account to make an accurate compari-

son, including labour, validation and quality. Selection of the cost minimum option depends on the specifics of the application and accurate accounting of the associated costs of each technology. Labour rates and process costing assumptions are taken from Biosolve cost modelling software (Biopharm Software Solutions). **Tables I and II** summarize the results of the cost analysis for a typical redundant filtration process using two 10 in. cartridges. The costs assumed here are representative of industry costs; it is assumed that difference in cost for utilities and materials (e.g., CIP solution, water for injection) does not significantly affect the cost comparison. The costs of pump and extractables–leachables validation are similar for both stainless steel and single-use setup, so these costs were excluded from the analysis.

SURF assemblies offer further benefits over stainless-steel setups. Equipment turnover for new products is quicker with single use assembly. For example, additional testing and cleaning time associated with equipment release and documentation is reduced or eliminated if single-use technologies are used. It also provides more production flexibility because single-use assemblies can be made to order in the size and configuration required with the need for additional equipment or validation. It also eliminates the need to have multiple setups in place to meet the production demands of different products.

Table I: Capital and validation cost. Capital and validation costs are taken over 10-year expected lifetime of the facility.

Category	Comment	Stainless-steel	Single-use
Hardware (assuming 2x SS assemblies)	Total cost + cost of capital (depreciation)	$20000 + 10% cost of capital	None
Validation	Design fee	$4000	None
	Hardware	$3500	None
	Cleaning including product carryover validation	$5000	None
	SIP/autoclave	$7500	None
Total		$69379.85 $6938/year $69.38/batch*	$0

Table II: Cost per batch. The cost calculations in this table are based on 12.5 h batch time for stainless steel setup and 6.5 h batch time for single-use assembly. The batch time is lower for single-use assembly due to elimination of preparation steps, cleaning procedure and ease of handling.

Category	Stainless-steel ($ per batch)	Single-use ($ per batch)
Capital and validation	69.38	0
Labor cost	2258.15	1174.24
Consumables	844.00	2067.00
Total	**3171.53**	**3241.24**

CONCLUSIONS

This study identified a suitable design for redundant filtration operations by utilizing single-use technology. An optimized utilization sequence for preparatory steps was designed and tested. Conducting a pre-use integrity test on a pre-sterilized redundant filtration setup can be challenging, but an effective filter wetting step is important to avoid false negative integrity test results. For high-value products, the drying step after integrity testing is crucial to minimize product dilution. All preparatory steps and filtration operations can be successfully performed on a single-use assembly. SURF assemblies are robust and efficient disposable solutions for bulk and final fill processes.

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Self-Administration of Injectables

Steven Kaufman, Mark Novara, Charles Potter, and Peter Sadowski

Industry experts discuss the benefits and challenges of self-administration of injectable therapies.

Maciej Frolow/Getty Images

Increasing numbers of biological drugs are being developed, driving a strong demand for innovative injection technologies. This need extends far beyond the traditional syringe, and companies are now packaging their biological products into more advanced products, such as autoinjectors. Although these devices may be more expensive than basic syringes, they offer the potential for patients to self-administer a therapy outside of healthcare settings.

The biopharmaceutical industry is under increasing pressure to justify the cost of therapies, particularly if they want them to be included in national healthcare programs. Self-administration is one way of significantly reducing costs and offers further benefits, such as being more convenient for the patient. Here, industry experts discuss the importance of self-administration and what technologies are best suited to this cause.

BioPharm: Why has patient self-administration of therapies become such an important driver in the healthcare and biopharmaceutical sectors?

Kaufman (SHL Group): Self-administration therapies have become an important driver in the healthcare and pharma sectors for a number of reasons. Empowering patients and giving them the freedom to take medications at home or while on the road is more than just a trend; it is vital to the economic viability of healthcare systems worldwide. Enabling patients to self-administer their medication means that healthcare practitioners can use their time more effectively. Most importantly, it has the potential to save money as fewer trips to the hospital can amount to millions in healthcare cost savings.

This trend has had a significant impact on the evolution of injectable drug delivery technologies. Many people are familiar with self-administered medications, such as inhalers for treating asthma, but few individuals, other than diabetics, have experience of injecting themselves using a syringe. As a result, drug delivery companies have had to develop devices that are both intuitive and safe. With the increasing

Roundtabe particpants include: **Steven Kaufman,** marketing director, SHL Group (Scandinavian Health Group); **Mark Novara,** worldwide director, Strategic Marketing, Self Administration and Injectable Systems, at BD; **Charles Potter,** chief technical officer at Glide Pharma; and **Peter Sadowski,** chief technology officer at Antares Pharma.

number of approvals for new biologics in recent years, demand will also be quite strong for autoinjectors and pen injectors. However, developing and producing an injection device that is safe, ergonomic, easy to use, and accurate enough for a patient to self-administer involves meticulous designs, innovative technologies and consistent manufacturing. For example, the spring mechanism inside an autoinjector controls the force and timing of the injection and is designed to accommodate the desired injection specifications, while the outer shell of the device may be affected in size and design by the primary container inside and human factor constraints. Once a proven mechanism is designed, ensuring consistent manufacturing then becomes vital because quality needs to be built into every device produced. At this time, there are only a few companies in the world that can design, develop, manufacture, and assemble these pen-like devices, and these companies will need to work closely with biopharmaceutical partners to ensure that patients get the best drug-delivery devices possible.

Novara (BD): There is a growing prevalence of individuals living with chronic disease in the world. However, the good news is that pharmaceutical medicine is working in order to keep pace with this increase. Advancements in therapeutic agents and medicine have resulted in the availability of more sophisticated biologics for the treatment of many chronic diseases. In addition, there is a growing trend in self-administration medicines where patients can self-medicate. This trend has supported the need for further advancement in self-injection technology.

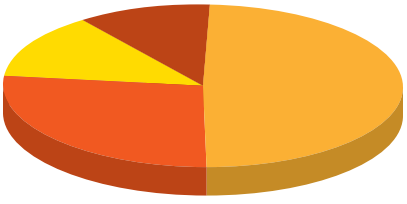
These biologics often have complex technical requirements for injection. For example, they have higher volume or are more viscous, so the technical specifications of these biologics are more challenging and require complex delivery technology. This trend explains why self-administration has become so important. In this respective, device manufacturers must be proficient in patient-centric design and should consider the ergonomic and human factors.

Integrating those biologics with the right delivery system has become critical, not only from a technical specification standpoint, but also from a competitive perspective. The competitive dynamics for new drugs in different fields will require different considerations in the selection of an injection device. Patient consideration is also a factor; for example, a patient with rheumatoid arthritis may have dexterity issues, requiring certain design specifications to make the device easy-to-use. In this respective, it's important for device manufacturers to be proficient in patient-centric design and to consider the ergonomic and human factors.

Integrating the primary container with the secondary device successfully is also critical. Companies offering self-administration technology need to have that expertise in order to improve performance of a drug-device solution, reduce risk of failure, and accelerate speed to market.

Potter (Glide): Rising healthcare costs mean that treating patients is becoming more and more expensive. If a patient can self-administer their medication then this reduces the time they need to spend with a healthcare professional and, thus, reduces cost. Most medications can be taken orally, but many peptides and proteins have to be injected to ensure they are not damaged by the acidic environment in the gastrointestinal tract. If a patient is to be trained to self-inject, however, then the technology needs to be simple to ensure that it is operated correctly. In addition, medication compliance is a serious issue with many patients; the easier and more convenient the product is to use, then the more likely the patient is to take their medication. These needs for lower cost of goods, ease of use, and convenience are also shaping the evolution in drug delivery technologies suitable for self-injection.

Which injection technology is gaining the most ground in the market?



Sadowski (Antares): Self-administered products currently account for about half of the of therapeutic biologics market. The simple reason for this is that more biological agents requiring injection are being used in chronic conditions, such as rheumatoid arthritis, psoriasis, and multiple sclerosis. Since it is both costly and inconvenient for patients to go to their healthcare provider to administer these biologics daily or weekly on a chronic basis, the burden falls upon the patient. Fortunately, technologies exist that make the self-medication process as comfortable and easy as taking a pill.

BioPharm: Which technologies are most suited for self-administration and why?

Kaufman (SHL Group): As patients are not medically trained, empowering them to feel comfortable enough to properly inject themselves requires a device that can make them feel safe both mentally and physically. To address this, devices with special features and technologies, such as the autoinjector, are often designed so the patient never sees the needle and may finish administering the drug within a relatively short period of time. While reactions to physical pain may vary for each patient, the mental pain connected to visually seeing a needle inject can be reduced,

Poll, Biopharm International online, 2012

especially when the patient also has control over when to initiate the injection. As a result, autoinjectors are becoming a commonly accepted drug-delivery technology for self-administrated injectable therapies.

However, it is important to note that each patient needs to be properly trained on how to use such devices and they must be provided with very clear instructions for use. The use of picture-oriented instructions and video has been a good step towards addressing this issue. Another potential drawback related to self-administration technology is the cost associated with developing a drug delivery device and the actual cost of each device. At this time, it is much easier for larger biopharmaceutical companies, which have the necessary financial resources, to initiate these programmes. Additionally, the market value of the drug must be able to justify the cost of the device.

Novara (BD): The most suitable technology depends on many factors:

- Technical specifications: A high volume or highly viscous biologic, which may be infused in a hospital setting, may require a patch injector/patch pump to deliver the medicine in the home setting. It is also important that careful consideration is given to the delivery of drugs that have a unique viscosity or volume that needs to be delivered.
- Competitive dynamics: Pharma and biotech companies are increasingly looking to their device as a source of differentiation.
- Patient factors: Certain patients will have certain needs and preferences given their condition and how mature that market is with devices.
- Frequency of administration: Whether a drug is injected on a daily basis, versus a weekly or monthly basis, is also an important factor (along with the cost factor).

All these considerations are crucial factors in selecting the right technology. For device manufacturers, it's important to have expertise across a range of delivery platforms and technologies in order to meet the above needs for customers.

Potter (Glide): Autoinjectors and pen-injectors have been designed for self-administration. These technologies are widely used, work very well, and are far easier to use and more convenient for patients than a standard needle and syringe. However, they still use a needle, which brings about issues related to needle reuse, needle disposal and needle phobia. In addition, many drugs that have to be injected are not very stable in a liquid formulation. Some biologics are stored in a powdered form to provide better stability, but they need reconstituted prior to injection, which adds to costs and treatment complexity. Liquid jet injectors avoid the issues with needles, but still incorporate a liquid formulation. They are also very expensive and have not achieved significant market traction.

None of the technologies mentioned really provide a simple way to inject a controlled-release formulation. Typically, a controlled-release formulation comprises polymer microspheres in a solution, but because of the issues of needle clogging these expensive products are normally injected by specially trained healthcare professionals. Other injection technologies, such as solid dose injectors and microneedle patches, are in development, but they are not yet ready for routine patient use.

Sadowski (Antares): The key to considering self-administration technologies is to focus on the patient. Our company, for example, is not committed to any particular injection technology type. Companies should design the technical solution that best fits the circumstances in a given therapeutic application. In particular, it's important to consider the patient's needs and limitations in the target disease condition, and then to look at how best to apply technology to make the patients' self-injection experience most acceptable and successful.

BioPharm: What extra steps do companies need to take to have a drug approved for use in a self-administrative form?

Kaufman (SHL Group): Generally, a biological drug will need to be first approved as an independent drug, regardless of whether or not it is to be used in a self-administrative form. For the device constituent of a combination product, the medical device manufacturer will generally support biopharmaceutical companies by filing a master access file and/or 510K to help with the customer's submission process.

Self-administered biological drugs can generally be placed inside a primary container such as a prefilled syringe or cartridge, which will then reside in a device that possesses the mechanical system to perform the injection. The two together are a drug/device combination product that, although not yet official, has been identified by FDA as an area that requires regulatory guidance. Companies that wish to introduce a drug in a self-administrative form will need to start regulatory planning at a very early stage to ensure that approval times do not become a potential bottleneck to a successful global launch.

Novara (BD): The complexity of clinical development and the regulatory process is increasing, and companies must take every appropriate step to ensure that their products are in full compliance. In addition, companies have to bear in mind the lead times for regulatory processes.

Potter (Glide): Any pharmaceutical product in development must undergo clinical trials. In addition,

a product that is to be self-administered needs to undergo trials with volunteers and patients to ensure that the delivery system can be safely used by different patient groups in a non-clinical setting. Some of these trials may be user-handling trials, with no drug involved, just to demonstrate that the volunteer can safely use the delivery system. These trials are far simpler and cheaper to conduct than active drug trials. Once trials have been carried out for a first product, then further trials to investigate the handling and use of the delivery technology may only be required if the product is for a different patient group (e.g., elderly patients or patients with rheumatoid arthritis who may struggle to handle a delivery device).

BioPharm: How are designers and manufacturers of self-administration devices approaching the challenges of ensuring sterility and accurate dosing outside of healthcare settings?

Kaufman (SHL Group): Accurate dosing is achieved through specially designed delivery mechanisms, rigorous testing, and precise manufacturing. For example, in a mechanical device, highly accurate dosing can be achieved using the appropriate spring technologies. Sterility is ensured again by designing a suitable device for the primary container selected by the biopharmaceutical partner; for example, a prefilled syringe that is assembled into an autoinjector under controlled procedures in line with related regulations and standards.

Sadowski (Antares): First, it is important to consider the fact that the product will be used without the direct supervision of healthcare professionals. Companies should conduct extensive background research and ethnographic studies to fully understand the patient and the likely environment of use. The design can be established based on the findings of the investigations and the pilot device can be tested with the patient in a variety of expected actual-use settings to confirm that the product will perform as intended.

BioPharm: The ability to offer adjustable doses, for example in diabetes, has great potential. What progress is being made in this area?

Kaufman (SHL Group): We see progress in the development of unique and robust mechanical designs that can accommodate the need to offer adjustable doses. This allows for the device to remain cost effective, as some drugs do not have a market price that justifies complex drug delivery technology. However, we do see a renewed drive to incorporate electronics into some of the more expensive devices, which is perhaps inspired by the trend of cutting-edge designs related to smart phone and tablet innnovations.

Sadowski (Antares): Technologies that provide dose adjustability have already been developed and commercialized. Cartridge-based, multidose pens, for example, have achieved excellent acceptance in the administration of insulin. Companies are now working on improving dose adjustability and confirmation of correct dose by applying advanced electronics that aid ease of use and add intelligent features.

BioPharm: What are the challenges of manufacturing devices suitable for self-administration?

Kaufman (SHL Group): Main challenges include anticipating numerous device usage scenarios against which to test the device, ensuring quality consistency, and providing robust production lines to respond to mass production needs. To address these challenges, device manufacturers should work closely with biopharmaceutical companies to better understand end-user feedback and use it to more accurately reflect and construct usage scenarios for device testing. In addition, device manufacturers need to continually invest in the latest in-house capabilities and processes.

Novara (BD): In most cases, customers will want some level of customization; they rarely want off-the-shelf devices. The challenge for manufacturers is delivering these differentiated customized devices at an affordable cost—for both the customer and the manufacturer. Companies are utilizing modular platform technology to develop and customize devices.

The market place is also uncertain and highly dynamic. Manufacturers are business-to-business organizations selling devices to pharma and biotech companies. If their business changes, suffers, or is impacted, so is that of the device manufacturer. This requires methodical portfolio management and operational planning to optimize the business.

When customers choose a device partner, they make device-based decisions, but also company-based decisions. They will be looking for factors such as a global reach and full service support, including support with global registration, and the ability to offer a differentiated benefit.

Sadowski (Antares): The most important aspect of making devices for self-administration is ensuring that they perform as intended in the hands of the patient. That means we need to first understand the patient. There are well-established ethnographic research methodologies that can be used to learn about patients and the environment in which they will use medicine. However, even today, many companies delay addressing this aspect in clinical programs. As a consequence, products have been launched in a configuration that is clearly not well suited for self-administration. Only later, after the product fails to meet market expectations, does the company initiate programs to address the

Agilent Technologies

needs of self-administration. It can be argued that keeping the configuration as simple as possible (e.g., in a vial) reduces development risk and cost,but this must be balanced against the resulting market risk, particularly when competitors introduce a product that better addresses self-administration challenges.

BioPharm: Needle-free devices seem to have lost some traction in the market, why might this be the case?

Kaufman (SHL Group): At this time, innovations in drug delivery devices with needles continue to move forward in addressing the growing need to administer biologics. Autoinjectors and pen injectors have been proven to be effective, safe and reliable devices. With this established track record, needle-based devices will continue to strengthen their position in the self-administration market.

Novara (BD): There are two factors that may have contributed to this. First, needle-free technology can be more complex, and there are various safety and operational challenges. Secondly, needles are now available that are very fine, as well as being shorter and less painful than previous generations of needles. Self-injection devices also continue to become more advanced.

Potter (Glide): The needle-free devices that have been commercialized are all liquid jet injectors. These devices work by firing a tiny jet of liquid through the skin. The concept was first patented many decades ago and niche products have been on the market for years. The products are either disposable devices or reusable actuators with a single-use drug component.

The reusable devices have been used in the past in the developing world and in the military for vaccine studies, but lost favour when the potential for cross-contamination between patients was identified. Single–use jet injectors are expensive and have never been widely used. I believe this is because the benefit of needle-free technology does not outweigh the increase in costs over alternative technologies. Liquid jet injectors will continue to be used for a number of niche products, but they will struggle to increase their market share. However, other technologies in development, some of which are needle-free, are likely to get good market traction as they are commercialized.

Sadowski (Antares): It's not a matter of needle-free having lost traction; it's a matter of the matching the technology to the needs of the patient population. I have no doubt that we will see greater applications of needle-free technology as additional biologic drugs are developed for populations best served by that approach, such as pediatric patients.

BioPharm: What recent groundbreaking innovations have you seen in the area of self-administration devices?

Kaufman (SHL Group): Groundbreaking is a powerful statement. I have seen a number of significant innovations in the area of autoinjectors over the past seven years, particularly when it comes to the look and the size of devices. Autoinjectors are more discreet and are now available in sizes that are not much bigger than a marker pen, which allows patients to travel and use the devices whenever and wherever they wish without feeling embarrassed. Industrial designers have also worked closely with human factors engineering groups to make several devices (launching soon) that are completely customized to suit the needs of a specific patient group. For example, if rheumatoid arthritis patients have difficulty removing a cap, industrial designers can overcome this by engineering a new solution for cap removal. These may not be groundbreaking, but to me they represent a significant shift in the way devices

are being made—working more with patients at the earliest stages and making drug delivery devices that are simple and intuitive.

Novara (BD): The innovations I am very impressed with are the patch injectors/patch pumps. This new technology is allowing companies to deliver therapies, which historically have been infused in a hospital setting, in the privacy and convenience of the patient's home. For example, technology is in development that can allow patients to have continuous infusion at home with a ready-to-use hands-free, device.

Potter (Glide): I believe that the two biggest innovations in the area of self-injection devices are microneedle patches and solid dose injectors.

Patches are being commercialized that incorporate tiny needles to aid the delivery of drugs and vaccines across the skin. The microneedles are either solid and coated in a film of drug; hollow to allow liquid formulations to be pushed through them and into the skin; or solid and made from the drug. The key is to ensure that the microneedles penetrate the skin so that the drug or antigen can be accurately delivered. Several companies are commercializing microneedle patch technologies and these will be suitable for the delivery of a range of peptides, proteins and vaccines.

Solid dosages are currently injected using a needle and trocar. This is a painful procedure and is not suitable for self-injection. Our solid dose injector technology differs in that a tiny rod of drug is produced with a point on one end so that it can be pushed into the skin without the need for a needle. When placed in the skin, the rod dissolves and releases the drug or vaccine into the tissue. Storing the drug in a solid dosage form offers stability benefits and may avoid the need for refrigeration. Solid dosages have been shown to dissolve quickly in clinical trials, providing bioequivalence compared with a subcutaneous needle and syringe injection. However, the formulations can also be designed to provide controlled release, if desired, by incorporating polymers in the formulation. The device is simple to use and could be used for self-injection. Most applications will comprise a small, low-cost, disposable cassette that will be prefilled with the drug or vaccine dosage, and a handheld, spring-powered, reusable actuator. The cost per injection will be low and the technology will be suitable for a wide range of peptides, proteins and vaccines.

BioPharm: What is your overall assessment of the future of injectable drug delivery?

Kaufman (SHL Group): With the wave of biologics coming to market, several new devices, such as autoinjectors, will see increased competition. One clear way that companies will differentiate themselves will be in the choice of drug delivery device. Designing, developing, producing and launching a biologic in an innovative device will not only enhance patient compliance, but could result in more revenue. For biopharmaceutical companies, the trend is clear: find the right partner, and develop devices for your biologics and future biologics now. It takes time and money, but it will be well worth it.

Novara (BD): The future is very bright. There is a steady increase in chronic diseases, but therapeutic developments are keeping pace by offering very sophisticated treatments that can be used with self-administration and injectable systems. However, there is an increasing need for differentiation and customisation of self-injection delivery solutions to help customers strengthen brand loyalty and to increase patient adherence and compliance with therapy. Device manufacturers with a broad portfolio of differentiating devices, full-service expertise, a commitment to quality-by-design, and global scale are uniquely positioned to meet the needs of pharma and biotech customers, payers, and healthcare professionals. Most importantly, injectable drug delivery systems afford a unique opportunity to patients with chronic disease to optimally treat their condition with minimal disruption to quality of life.

Potter (Glide): Biologics is one of the key growth areas in the pharmaceutical industry. Biologic products typically need to be injected and injection technologies will be required for these products, whether they are new products or lifecycle management strategies of existing products. I believe that there is a fantastic future for injectable drug delivery technologies. In particular, those technologies that can deliver a range of drug and vaccines, and that are suitable for self-injection and have a low cost of goods, will be used to develop products for both existing drugs and new drugs in development.

Sadowski (Antares): Pharmaceutical pipelines are increasingly reliant upon biological products and the range of therapeutic applications for biologics is expanding to chronic conditions. We are also seeing improved cancer survival rates, in part due to improved, targeted biologic therapies, which mean that cancer will be treated more often as a chronic condition using self-injected biologic therapies. Cost pressures and patient preferences will drive pharmaceutical firms to shift the administration approach from higher cost settings, such as infusion centers, to self-administration. All of this will expand the range of therapeutic applications for self-injected products, leading to greater reliance upon and advances in technologies suited to meet the needs of increasingly diverse patient circumstances. ◆

Biosimilars

Structural Characterization and Comparability Approaches

LIVE WEBCAST
April 26, 2012 at 11:00 AM EDT (North America)
and May 3, 2012 at 11:00 AM CET (Europe)

Register free at http://www.biopharminternational.com/structural

EVENT OVERVIEW

The regulatory pathway for biosimilar products, the Biologics Price Competition and Innovation Act, was approved in 2010 in the United States, and FDA has recently issued draft guidance for the industry to bring a biosimilar to market. In Europe, EMA has had a pathway in place since 2005 and has approved approximately 14 biosimilars to date. Also on the biosimilars regulatory landscape is the International Conference on Harmonization's Q6B guideline on test procedures and acceptance criteria for biotechnological/biological products. As industry moves forward to develop, test, and market new biosimilars at the global level, structural characterization of these products according to regulatory expectations will be crucial.

This webinar will provide information on how to approach biosimilar characterization and comparability to originator molecules. In addition, the webinar will provide an overview of the current regulatory expectations and plans for biosimilars in the US and European Union.

Key Learning Objectives:

- Hear from industry peers about best practices and technical solutions in biosimilar characterization
- Gain an understanding of US and European regulatory pathways for biosimilars
- Learn about comparability studies for biosimilar products

Who Should Attend:

- Biopharmaceutical experts engaged in formulation, analysis; QA/QC and regulatory personnel; BLA and marketing authorization applicants; biopharmaceutical managers and laboratory scientists entering or planning to enter the biosimilars market

Presenters:

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Knowledge Management Implementation in a Biopharmaceutical Company

Tarun Jain and Bipul Pandey

ABSTRACT

Knowledge Management (KM) is one of the most important systems for any biopharmaceutical company. KM is considered to be a vital connection between other management subsystems in an organization. This article focuses on the steps needed for successful implementation of KM in a biopharmaceutical company. The KM implementation discussed here enables new possibilities of effective usage and allows exploration of valuable information existing in a company. The article also emphasizes the use of an electronic document management system (EDMS) and the implementation of other such innovative information technolgy tools. Case studies from the biopharmaceutical industry are used to illustrate the KM implementation methodology.

The biopharmaceutical sector is a knowledge-intensive domain where the emphasis is on continuous product enhancement to meet the current market demand. Organizations are discovering that they need to do a better job of capturing, distributing, sharing, preserving, securing, and valuing their knowledge to stay ahead of their competition (1). The ability of companies to exploit their intangible assets has become far more decisive than their ability to invest and manage their physical assets (2). By managing its knowledge assets, an enterprise can improve its competitiveness and adaptability and increase its chances of success. With an increasing elderly population that consumes three times as many drugs as younger consumers, expansion into developing regions, and an overall increase in population and lifespans, the annual sales of the pharmaceutical industry have increased. Equally encouraging for drug companies is an evolving product pipeline. Process development of novel drugs, improved technology and laboratory research techniques, genomics, proteomics, and increasing R&D investments are shaping sophisticated research data systems. However, there are regulatory concerns, branding issues, impending patent expirations, escalating R&D and operations costs, and an increased complexity in research data that can result in information overload.

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PEER REVIEWED

Article submitted: Oct. 25, 2011.
Article accepted: Dec. 5, 2011.

Table I: Data encountered by key personnel in the biopharmaceutical industry.

R&D scientist	Scientific manager	Production engineer
Raw text	Raw text	Raw text
Email messages	Email messages	Email messages
Patents	Project reports	Product sampling schedule
Research papers	Spread sheets	Materials transfer record
Spread sheets	Research experiment records	Process flow sheets
HTML documents	Patents	Regulatory guidelines
Lists	Research papers	QA/QC reports
Equipment system generated reports (eg., chromatography systems)	Laboratory scientist's payroll and appraisal data	Standard operating procedures (SOPs)
Data from biological databases (e.g., PDB)	Technology transfer documents	Raw material management data
Standard operating procedures (SOPs)	Regulatory guidelines	Product mass balance and yield data
Instrument manuals	Financial and budgeting data	System calibration reports
Instrument log Books	QA/QC reports	Instrument manuals
Data of ongoing experiments	Development reports	Plant executive's workflow and shift records

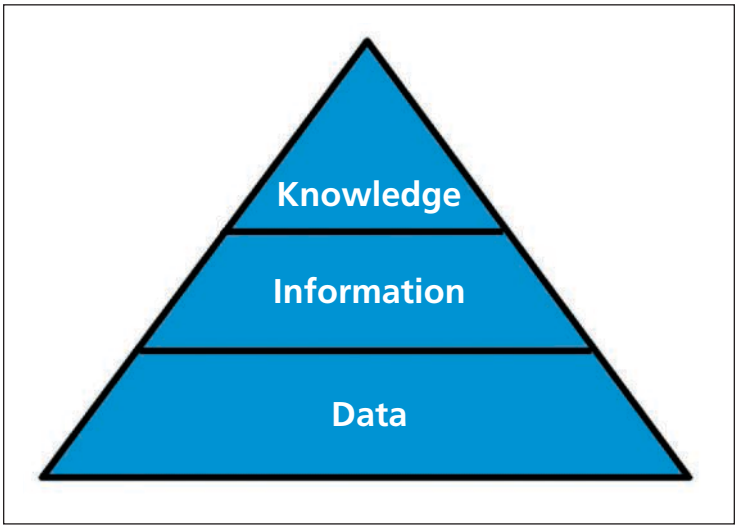
Opportunities in the pharmaceutical industry have never been brighter, but only if companies can harness their knowledge to make better decisions faster. Knowledge management (KM) is a crucial component of any life-science research company. Without an effective knowledge management strategy, it is difficult for a company to quickly respond to current market demand. KM assists in improving research methodologies, maintaining process flow, and ultimately cutting overall costs. This article focuses on the technology and guidance required to achieve good KM in a biopharmaceutical company.

KNOWLEDGE MANAGEMENT AND RELATED CONCEPTS

Knowledge

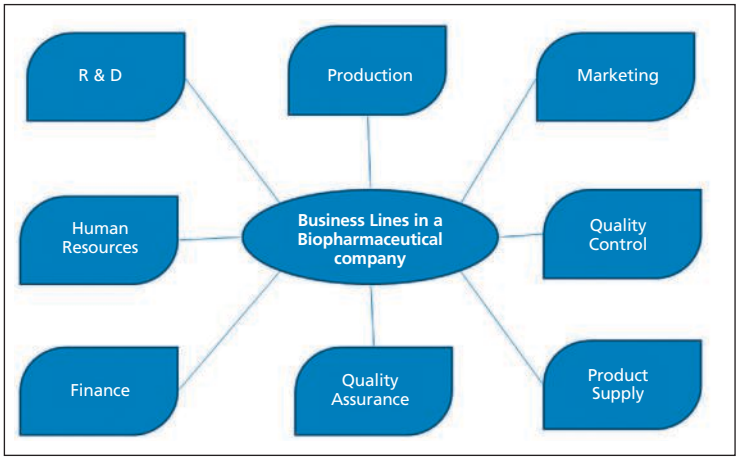
According to Davenport and Prusak, knowledge is located at the apex of the three-story pyramid (see Figure 1) (2). At the first level of pyramid is data, which expresses objective statements in terms of a transaction record (3). For example, the reading of a pressure gauge in a depth filtration process is a datum. The second level of pyramid is information, also called the message. To transmit a message, there must be a sender, a receiver, and a package of information created by the sender. For example, the reading of the pressure gauge can be converted into information by comparing it with standard values and pressure, and can be thus be attributed as high or low pressure. Knowledge is located at the third level of the pyramid. Obviously, it is more general than data or information, but still needs these two as a foundation. Knowledge stems from information just as information originates from data. For example, consistent high pressure above a certain value, for example, 3 psi, gives the user knowledge that a given depth filter will fail as soon as pressure reaches 3 psi.

Figure 1: Identification of data and information in the company.



ALL FIGURES ARE COURTESY OF THE AUTHORS

Figure 2: Various business lines in the biopharmaceutical industry.



Knowledge management

Knowledge management has emerged as an area of interest in organizational practice. According to Malhotra,

> *"KM embodies organizational processes that seek synergetic combination of data and information processing capacity of information technologies, and the creative and innovative capacity of human beings (4)."*

Backman defines KM as

> *"the formalization of and access to experience, knowledge, and expertise that create new capabilities, enable superior performance, encourage innovation, and enhance customer value (5)."*

Thus, KM can be defined as a systematic management of all activities and processes referring to development, storage, sharing, and utilization of knowledge for an organization's competitive edge.

Reasons for knowledge management implementation

The amount of data that a person in pharmaceutical company handles is extremely large and is rapidly growing. Table I shows data encountered by different people in a typical biopharmaceutical company. Looking at the complexity of data faced by people at different levels, adoption of KM in the organization becomes imperative. A successful KM approach helps to better organize data, which further facilitates data analysis and interpretation. Furthermore, the business environment is getting more demanding because of a number of factors, including:

- Increasing number of competitors
- Market requirement of drugs
- Increase in number of antibiotics, vaccines, and biosimilars
- Advancement of technology
- New regulatory guidelines.

This complexity has made it important for an organization to respond quickly and effectively to changing environmental conditions. To maintain a competitive advantage, a company's data must be structured in a traceable way. This can be achieved through the implementation of KM in an organization.

Crucial factors for success

There are several key variables for successful implementation of KM. They are as follows:

- Employee learning and development
- Organizational infrastructure
- Technology infrastructure
- Knowledge-friendly culture
- Senior management support and commitment
- Information-systems infrastructure
- Teamwork
- Knowledge structure.

KNOWLEDGE MANAGEMENT IMPLEMENTATION PROCESS

Phase 1: Identification of data and information

In a typical biophamaceutical company there are various business lines as shown in Figure 2. The first phase of the KM implementation process includes conducting brainstorming sessions at several randomly selected meetings at different levels with different business lines such as R&D research group meetings, individual personal dialogue, or meeting with production officers. Through these meetings, information and data that are not yet recognized and systemized can be identified. For example, meeting with a production officer to discuss various process parameters of a chromatography process may help to monitor and record these process parameters in a systematic way, or meeting with a research group to discuss the characterization process of a particular

Figure 3: Implementation of data access control strategy.

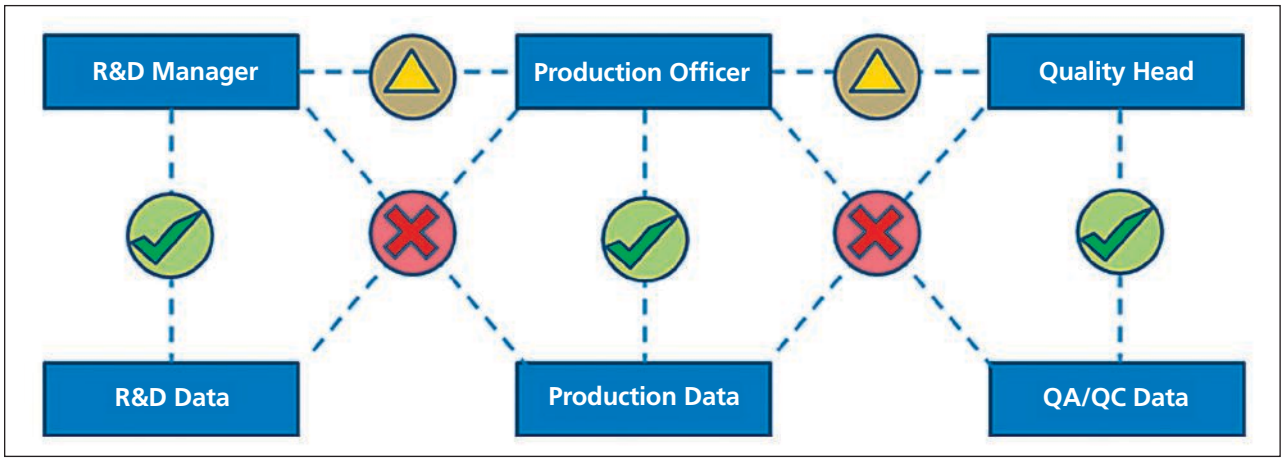
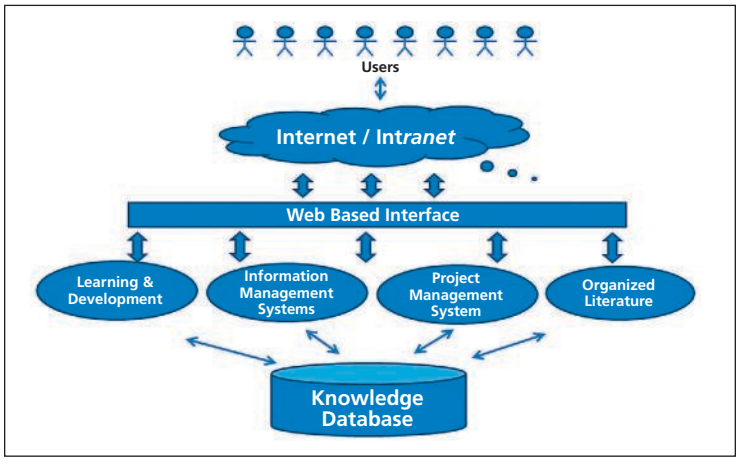


Figure 4: System structure of knowledge management.



molecule may aid in the documentation of the characterization process in a systematic way.

Phase 2: Identification of data storage process

This phase involves identification of various processes being followed by various people at different business lines. The process includes going through existing standard operating procedures for different processes, or examining process flow sheets and finding how the data is being stored.

Phase 3: Identification of data storage location

Based on findings from phases 1 and 2 the data locations are identified and listed. Storage locations can include corporate databases where relevant data is stored in the organization. These locations can be computer hard drives, USB drives, CD-ROMs, paper files, or corporate databases.

Phase 4: Classification of structured and unstructured assets

Data from various locations can be categorized as structured and unstructured assets. The structured assets are data that are stored in several database tables within specific applications according to the need of a particular business line. Typical examples are chromatography system software for storage of process information, chromatograms and reports of a particular chromatography process, or ERP systems for materials management. The data that are not stored in several database tables within specific applications are unstructured assets. Unstructured assets can be divided into documented and undocumented assets. Documented assets are unstructured assets stored in various process templates, or spreadsheets. Undocumented assets are unstructured assets which are not stored in anywhere in an enterprise. A typical example of an undocumented asset is expert knowledge that a process consultant stores in his brain.

Phase 5: Transformation of data and information into knowledge

This phase deals with organizing the data and information and converting them to

knowledge-rich information systems. An example of such an information system is an electronic document management system (EDMS). The EDMS manages electronic documents, scanned documents, pictures, tables, and other types of data. It enables efficient search, controlled storage, data security, data sharing, and data nonredundancy. Furthermore, these management systems enable secured access through different business lines. Consider a case as shown in Figure 3, where data is to be shared between quality control, R&D, and production managers. In this typical case the R&D manager can directly access the R&D data but can't access the production data. If he needs to consult any production data, he can access the data via access procedures through a production officer. A similar interaction can be described between a quality head and a production head.

Phase 6: Proposing the system structure
This phase includes providing IT solution by creating a KM framework. This stage mainly deals with proposing the the system structure for KM. A typical example of such a framework is shown in Figure 4, where the user (e.g. R&D person, Finance officer etc.) interacts with a web-based interface through the internet or intranet. The Interface is designed in such a way that it is connected to all information management systems (e.g., enterprise resource planning, project management systems, learning and development modules, etc.) All information management systems, project management systems, learning and development modules, literature modules, and so forth, are connected to a database at the backend. This approach helps in effective data mining and prevents data redundancy and data overload.

Phase 7: Implementing the system structure
This phase includes the development of the system structure of KM. The development is carried out taking software development life cycle models in consideration. After development, the software is tested vigorously followed by maintenance. To implement the software solution of KM, various training sessions need to be conducted where people in the organization can understand the importance of KM, learn to implement KM through software solutions, and explore other issues regarding KM.

CONCLUSION

A KM initiative is a major concern for biopharmaceutical companies worldwide. The major objective of this article is to present the conceptual implementation of a KM framework for the biopharmaceutical industry. The framework, when implemented, will enable effective storage and handling of knowledge developed within the organization. This will also lead to more efficient process implementation within an organization as the knowledge thus achieved can be applied synergically throughout the organization when needed. This could go a long way in dealing with the various challenges being faced by biopharmaceutical companies.

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Growing Your Biopharmaceutical Product Pipeline

Key business considerations when starting out.

BioPharm International speaks with Tarja Mottram, CEO of Action for Results, regarding some of the deeper business considerations for companies aiming to grow a biopharmaceutical product pipeline. Action for Results is a life sciences-focused consulting company. The company helps to build process capabilities and the practices needed for innovation.

BioPharm: What's your take on the current industry dynamics?

Mottram: R&D productivity, especially in pharma, is way below acceptable. Despite increasing investment, the value generation curves don't seem to be getting much better. We could blame increased complexity—clinical, regulatory, global—or point to advancing technologies, which keep raising the bar. Or, perhaps we need to pause, step back, and look at different ways of working with one another and focus on the industry in a different way.

One thing I'm seeing is a global shift in life sciences from a traditional product development and manufacturing efficiency approach to focusing on evidence-based healthcare outcomes. As a result, the industry is reorganizing itself in the way that it partners with others, and the way that it works with customers and end users. In this time of learning comes opportunity. Some of the old models aren't going to work anymore. New organizations with great collaborative capabilities can really make a difference in this regard.

Tarja Mottram, CEO of Action for Results.

WEIGHING EXPERIENCE LEVELS

BioPharm: A lot of industry innovation comes from smaller start-ups and academic-based companies, and they are looking for ways to move from discovery, through development, and into commercialization. Business models and plans are key to their success. What has been your experience in working with early-stage companies?

> As an organization becomes successful, the commercial pressure settles in.

Mottram: It's an interesting topic. There are traditional maturity models that many consulting companies are offering to go from maturity level 1 to 2 to 3 and so forth, but I find it difficult to follow a maturity model and say, 'Okay, if you do these three steps, you're going to be golden.' There is wisdom in the maturity models, but it's important to customize the journey.

Take this example, which must be considered from two different dimensions. One dimension is the experience level or the maturity of the company in product delivery. Has the company actually put a product out to the marketplace, or has it already put two or three or four products out to the marketplace? At a personnel level, if the company is about to launch its first product, is there anyone with experience in product delivery leading the group?

The other dimension is the pipeline, that is, the company's volume or capacity to deliver. At the beginning, when there's no product out in the market, the company

Sveta Demidoff/Getty Images

tends to operate in a free-style entrepreneurial environment. Everybody pulls together to get the funding and other things the company needs, when it needs them.

As the organization becomes successful, the commercial pressure settles in. Often, in that excitement, the smaller companies or the medium-sized companies tend to lose sight of the fact that they have to start building capability—what was easy to do with one or two products has to be repeatable and sustainable over a portfolio of products.

The shift needs to be systemically thought through and put in place. Some companies set a series of milestones and maybe yell a little harder to make sure those milestones are met. The company keeps meeting their milestone miracles, but at some point, the organization reaches its limit, especially if it moves from one site to multiple sites. When complexity increases, the realization sets in that the basic capabilities—the real foundation for growth—may be missing.

Small companies can learn a lot from others who've already been there. This knowledge exchange can create a better balance from the start as the company maps out what it needs to do to get ready for growth.

MAINTAINING A LONG-TERM VIEW

BioPharm: How can a start-up company best digest this type of long-term view?

Mottram: Building strategic capability is a key, not just for small companies but also for the larger companies. We tend to be reactive by nature, especially in this industry. So if you are a start-up company, first understand where you fall within the industry and what problems your product can solve that others cannot. Think about the product's life cycle. It can take several years and lots of investment to move forward. How will you create value? This thought process demands a longer-term view—even for just one product. Companies need to think about what the world will be like by the time their product reaches the marketplace.

So, how do you create those sensing mechanisms in your organization that allow you to maintain a long-term view? If you start differentiating between winning companies and average companies, then long-term views become even more important. Winning companies are measured by their sustainability (i.e., the ratio between their R&D investment and the number of products that go to market).

> Winning companies invest in building top scientific leadership and in bringing customer and clinical insights together.

Winning companies are distinctly different from average companies. They don't just invest in traditional market research. They invest in building top scientific leadership, capable of deep thought around what the future will hold; they bring

customer and clinical insights together to address unmet needs. But, they don't jump into responding to an unmet need. Instead, they think thoroughly about what is needed and where their strength lies. This is an important element of success because when we talk about sustainable value over time, ultimately, the value is measured by the healthcare outcomes generated for the healthcare system.

For the business, the value also lies in what the business can produce in a successful way, so that it can stay in business. It therefore becomes important to marry the science and the business inside the company for a longer-term view and to become much more targeted in thought process and strategic thinking.

At this stage, the company should no longer be focusing on launching the next product, but rather, about what the impact of that product will be. This approach forces a portfolio view—even within a therapeutic area.

ADDING THE BUSINESS ANGLE

BioPharm: Introducing a business element to the R&D side can be complex. How can a company marry these two things together, as you mentioned, and demonstrate that both remain efficient?

Mottram: At the front end of the product development or innovation cycle, the focus is on finding the right product candidate to meet certain unmet needs in the market. Those needs should be driven by a clinical-need and market perspective because there are a million companies potentially trying to go after the same need. How do you make that area yours? What's the opportunity? What outcomes are possible? In the end, science rules.

By that, I mean it's not just about science. But if a company doesn't get it right, doesn't get that scientific foundation right upfront, then it won't find a way to differentiate itself in a truly affective way. Different factors come in to play, including understanding what clear success criteria looks like, evaluating risk tolerance, accelerating the proof of concept, and more. That's how the foundation is set. It needs to be scientifically sound.

The science doesn't go away, but at some point, the company starts to think about making major investments.

Business comes into that discussion because, obviously, the company needs to validate the proposed need and commercial value. But I would suggest that it's not until a company gets through that early process, that the focus starts shifting. The science doesn't go away, but at some point, the company starts to think about making major investments. The closer one gets to clinical trials, those investments get bigger and bigger.

Here, the business plays a much larger part in driving the right value along with the right medical outcomes. The other way to think about this stage is that that there is an increased focus in efficiency as a company goes through development; this phase introduces a new business element into the review and governance process.

Finally, if the company reaches commercialization, it needs to shift its attention to optimizing the impact of its product in the marketplace. It's important to understand these different stages, and to understand that they're integrated.

Start with the end in mind and what your company is trying to achieve in the marketplace. Be clear about the scientific opportunity. Based on that information, define the best development and commercialization path. That's what marrying business and science is all about. ♦

This article is Part 1 of 2. Part 2 will appear in the May 2012 issue. You can listen to the full interview with Mottram as a podcast online at: www.biopharminternational.com and click on Drug Development Basic Training.

Key Takeaways

- Understand the marketplace and the impact of your company's product on healthcare outcomes.
- Maintain a long-term view of your product's life cycle.
- Integrate a scientific foundation into any business plan.

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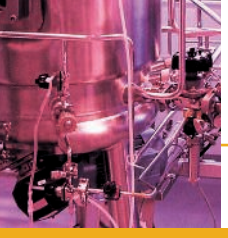

Small Changes, System-Wide Impact

A closer look at elastomer changeout times provides one example of using industry knowledge to improve operations and cost.

The butterfly effect is a much cited phenomena where a small change in a system can have a significant effect on the overall state of the system. In a similar way, relatively inexpensive elastomers can contribute disproportionately to the cost of running a biopharmaceutical manufacturing operation.

Elastomers and plastics play a vital role in the operation of a bioprocessing plant, forming gaskets, "o"-rings, and diaphragms deep within the structure of the processing equipment. Their function is to prevent leaks and to separate fluids that should never come into contact. These rubber-like materials are useful because they are flexible, elastic, and can ensure tight seals between hard metal surfaces.

Over time, and with the harsh temperature, chemical, and pressure cycles that they are subjected to, these materials can become brittle and deformed, and can fail. They need to be exchanged well before there is a risk of failure, the consequence of which could be a contaminated product or a dangerous breach of a system. Many biopharmaceutical plants have a large installed base of valves for example, maybe 5000 or more. Each one needs to be maintained correctly to avoid problems.

Simon Chalk is director of the BioPhorum Operations Group, simon@biophorum.com

Although the cost of failure is high, the cost of exchange is also high. It is estimated that up to 50% of maintenance activity is consumed by soft parts changeout. Add this to the plant downtime and there is a clear target for cost-saving scrutiny. So, what scope is there for improvement? Can current practice be challenged?

The currently accepted and common approach for elastomer changeout is temporal based (i.e., there is a fixed frequency—perhaps annually or biannually—for scheduled maintenance to replace the component).

> One can trace a direct line from one engineer to a new industry system of standards.

Although this approach is acceptable, it does not take into account the conditions that the elastomer has been subjected to. In cases where the component has been lightly used, it may be exchanged even though continued use would be perfectly acceptable. At the opposite end of the spectrum, severe use could risk failure of the elastomer before its fixed time period had been reached.

Several engineering leaders in biopharmaceutical operations are questioning this methodology. They are being driven by the unrelenting quest for operational excellence and more effective ways of working. As well as cost savings, there is the realization that their talented engineers could be better deployed working on high value-adding technical projects rather than routine maintenance.

One such engineer got into the habit of collecting discarded soft parts from changeovers and visually inspecting them. His curiosity and dislike of waste led him to ask whether there was a better way to systemize the replacement of these items so that they were used for longer but without risking failure in operation. His involvement in a cross-industry benchmarking group and discussions with his like-minded peers showed that better practices

Icon Image: Refine Technology

did exist. This knowledge spurred him to implement a new way of working, leading to significant cost savings.

By following simple scientific and risk-based approaches, some companies are now extending the life of elastomers by three, four, or five times. The previous time-based maintenance cycles have been replaced with condition-based cycles whereby the wear and tear on the components are carefully analyzed and graded so that the life of the components can be accurately predicted. The factors affecting wear and tear, such as the numbers of cleaning cycles, temperatures and chemicals used, are recorded to provide a rational basis for analysis and later, measurement.

Operational data showing variations from predicted results are further sources of insight, shedding light on unknown factors that lead to variability reduction and greater confidence levels predicting component condition. One such root-cause analysis revealed that correct or incorrect assembly of diaphragm valves can contribute significantly to performance of the soft parts. Correct lubrication of fixing bolts and accurate torque setting for instance was discovered to be a contributory factor in the life of diaphragms.

The question of conformance to specification was another target-rich area with lack of clear standards and nonexistent or inconsistent industry wide test methods. Elastomer suppliers have a long way to go to meet the exacting needs of the biopharmaceutical environment. Performance has historically been the customer problem. Lack of control around changes being a particular concern where the supply chain of suppliers and suppliers suppliers is not rigorously managed.

The same industry best-practice sharing group is now advancing the cause by proposing customer centric standards covering generic-test sequences, visual inspection criteria, and better change control. With agreement by the various stakeholders, these standards will be written into globally recognized codes that set the scene for better industry compliance.

In this example of a drive for best practice in biopharmaceutical manufacturing, one can trace a direct line from one engineer examining the disassembled parts of a butterfly valve to a new industry system of standards and quality performance levels previously not experienced. ◆

TUBING ASSEMBLIES FOR HIGH-VOLUME FLOW RATES

Meissner's BioFlex tubing assemblies provide secure and convenient fluid paths for use within single-use systems and are designed to accommodate flow rates in excess of 100 L/min. The assemblies can also be used in conventional or hybrid facilities to connect single-use and stainless-steel processing equipment. BioFlex assemblies are easily customizable to end-user requirements and can integrate sterilizing- through clarification-grade capsule filters.

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BIOPROCESSING HOSE FEATURES FLEXIBLE DESIGN

Saint-Gobain's Sani-Tech Ultra-HP hose is designed for the life-sciences market. Its USP Class VI-compliant hose materials include reinforced layers of Sani-Tech Ultra silicone bonded to an ultra-smooth PharmaFluor FEP inner liner to ensure optimal flow and ease of cleaning. This hose is lightweight and extremely flexible. Its applications include bioprocessing, load cells, and product transfer.

The Sani-Tech Ultra-HP hose is available in 12-ft. lengths, and is constructed with multiple layers of reinforced Sani-Tech Ultra platinum-cured silicone. It contains a smooth inner bore for improved cleaning and sanitization, a fluoropolymer liner to minimize the binding of biological materials, and high-purity materials with a low count of total organic carbons, extractables, and leachables. Additional features include a broad chemical resistance, a simple assembly procedure, and a temperature rating of –65 °F (–54 °C) to 350 °F (177 °C).

Saint-Gobain Performance Plastics
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MICROENCAPSULATORS IMMOBILIZE ACTIVE INGREDIENTS

Büchi has launched two new systems, the Encapsulator B-390 and B-395 Pro, for the immobilization of active ingredients. Both systems enable enzymes, drugs, vitamins, oils, and animal cells, as well as flavors and fragrances, to be encapsulated into polymers. The procedure is based on the principle that a liquid jet breaks up into equally sized droplets by superimposed vibration.

The particle diameter is preselectable in the range of 150 to 1000 µ with a narrow standard deviation and high reproducibility. Productivity is typically 500 to 2000 beads per second, and the system also provides continuous capsule generation. In addition, both encapsulators feature a user-friendly design.

The systems are suitable for animal cell encapsulation and maintain full viability of the encapsulated living material. Bead formation is reproducible and is real-time controllable in the light of an incorporated stroboscope lamp. The Encapsulator B-395 Pro provides sterile working conditions.

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Location: Singapore
http://www.interphexasia.com

JUNE

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Location: Philadelphia, PA
www.worldpharmacongress.com

11–12: 7th Annual Global Pharma Manufacturing Summit
Location: NJ Expo Centre, NJ
www.gpmsummit.com

11–12: World Vaccine Congress Asia
Location: Waterfront, Singapore
www.terrapinn.com

18–21: 2012 BIO International Convention
Location: Boston, MA
http://convention.bio.org

24–28: DIA 2012 48th Annual Meeting: Collaborate to Innovate
Location: Philadelphia, PA
www.diahome.org

JULY

9–12: 2012 Workshop on Protein Aggregation and Immunogenicity
Location: Breckenridge, CO
www.aaps.org

For event details and a complete calendar list, visit www.biopharminternational.com/events

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CELL LINES

LAB EQUIPMENT

Airflow Diagnostic Tools

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large and expensive clinical trials (2). Additionally, the situation is complicated by a shift in the balance of power among industry stakeholders, each of which may require different evidence to be convinced of a product's value.

Instead of thinking big, innovators need to think small. If a company shrinks the denominator to just the segment of the market that genuinely benefits, then the value element starts to look a lot better. This shift can mitigate business risk, as well. Rather than seeking a single indication for one, large group of patients, the rolling blockbuster approach for orphan drugs segments the market for a drug more minutely, creating a large number of target populations in which the drug's value can be assessed. Such an approach reduces the risk inherent in clinical trials because the binary outcome (reimbursed/not-reimbursed) applies only to the small segment under consideration. The population becomes the sum of those small segments, eventually comprising a much bigger population.

Compared with the bleak landscape of aging blockbusters, the orphan-drug market is appealing, especially when considering drugs that successfully made the leap from orphan to rolling blockbuster. Take, for example, Botox—a drug approved with orphan status in 1984 to treat uncontrolled blinking, neck pain, and muscle spasms. Since then, FDA has approved numerous additional indications, including the treatment of frown lines (2002) and migraines (2008). Today, there are 5 million doses of Botox administered annually in North America, which translates into approximately $1.5 billion in sales.

PRODUCT-DEVELOPMENT IMPLICATIONS OF ORPHAN DRUGS

Orphan drugs have historically focused on a small, defined market need. Because the population of individuals likely to optimally benefit from any individual drug may be small, drugs produced will be higher cost because drugmakers will have to recoup their investment from a smaller population of patients. Proving the economic and clinical value of treatment is therefore more crucial for orphan drug. This value case can include elements such as high quality outcomes, better patient experience, sufficiently improved health to allow the patient to more effectively manage other conditions, or product characteristics that improve overall patient adherence. Each of these elements should be explored and planned for early in product development.

Because the target population will be smaller, clinical-trial participants may include some people suffering from comorbidities that would otherwise be excluded from the sample. In this regard, the trial participants begin to look more like people in the real world. As a result, careful tracking of all patient outcomes will be crucial. Preparing to track these outcomes will need to start early in product development and continue postmarket to develop the kind of longitudinal data required to make the case for premium reimbursement rates to payers.

Finally, developing more targeted drugs alongside similarly targeted diagnostics will be key. As medicine becomes increasingly personalized and diagnostics become more targeted, it will become easier for orphan-drug makers to identify the population most likely to benefit from their drug. Developing drugs and diagnostics together will not only improve the likelihood that the drug will be successfully used, but can also improve the likelihood that the drug will be approved. In 2011, two personalized drugs were approved for use in conjunction with a specific diagnostic test— Xalkori (crizotinib) for lung cancer and Zelboraf (vemurafenib) for melanoma (3, 4).

A MODEL FOR SUCCESS

The advantages and benefits of adopting an orphan-drug centric approach reach beyond product development because the smaller population doesn't require large marketing or promotional campaigns. As a result, companies pursuing orphan drugs have adopted different kinds of promotional campaigns, often partnering with patient advocacy groups to get in front of their target populations.

This kind of commercial model could become the model pharmaceutical manufacturers adopt increasingly across their portfolios. Orphan-drug manufacturers have historically had to develop a deeper understanding of that population's characteristics than drug companies seeking blockbusters. As diagnostics become more targeted and the use of personalized medicine grows, companies pursuing all types of drugs will need to understand their target populations better and partner with advocacy groups like orphan drug companies have done. Ultimately, the growth of orphan drugs is one element of a larger paradigm shift in the pharmaceutical industry—one that manufacturers will need to adjust to.

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The Growing Orphan-Drug Paradigm

How niche strategies can offer mainstream potential for biopharmaceutical companies.

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Historically, orphan drug development has existed on the margins of R&D spend, but increasingly, this product class is attracting attention and value. With the blockbuster model wearing thin, the pressure for lower cost drugs with better outcomes is growing. It's time for the industry therefore to diversify its strategic approach.

The benefits of shifting focus to orphan drugs are many, including a streamlined approval process, patent extension and exclusivity, tax credits, and smaller clinical trials based on narrow indications. But as competition moves into these niche spaces, everyone will be looking for an opportunity to get an orphan-drug designation (ODD). This strategy may lead to additional scrutiny and intensify the need to demonstrate the economic and clinical value of a product as it applies to a particular population before approval.

The pursuit of orphan drugs has implications for change across the entire business. It will require a new R&D approach that addresses economic and clinical value data, and goes beyond randomized clinical trials for regulatory approval to alternative types of data (e.g., observational or "real-world" studies that demonstrate product value over time in real-life scenarios). Companion diagnostics used to identify the patient population most likely to benefit from orphan drugs represent another key area that biotech and pharmaceutical developers will need to explore. This area may present licensing and acquisition opportunities on both sides.

The growing emphasis on orphan drugs and more targeted diagnostics represent an increasingly personalized approach to medicine in general. An inevitable impact will be shrinking target patient populations, where the majority of blockbuster drugs will be suitable for a significantly smaller group of patients, the number of whom may well fall within the definition of rare diseases (6–8% of world population) (1). As genomics define specific subpopulations within larger disease conditions (e.g., hypertension), bio/pharmaceutical manufacturers of all sizes will increasingly need to shift to thinking about drug development within the context of the orphan model.

> Rather than seeking a single indication for one large group, the orphan-drug approach segments the market for a drug more minutely.

In this context, companies will have to seek indications for their products within narrower patient populations and build a large population of patients incrementally, rather than as one single, huge population used in the rolling blockbuster model. To develop a successful model based on orphan drugs, manufacturers will need to adopt a new approach to both product development and commercialization.

ADVANTAGES OF THE ORPHAN-DRUG PARADIGM

Rising product development costs, stingier public and private reimbursement, and increasing regulatory hurdles mean that companies are struggling more than ever to bring new products to market at prices that sustain ongoing investments in innovation. Ongoing waves of blockbuster-drug patent expirations are offering insurers cheap and effective generic drugs. Concurrently, rare but significant side effects (as in the case of Vioxx) have eroded regulators' willingness to approve drugs for primary care indications without prohibitively

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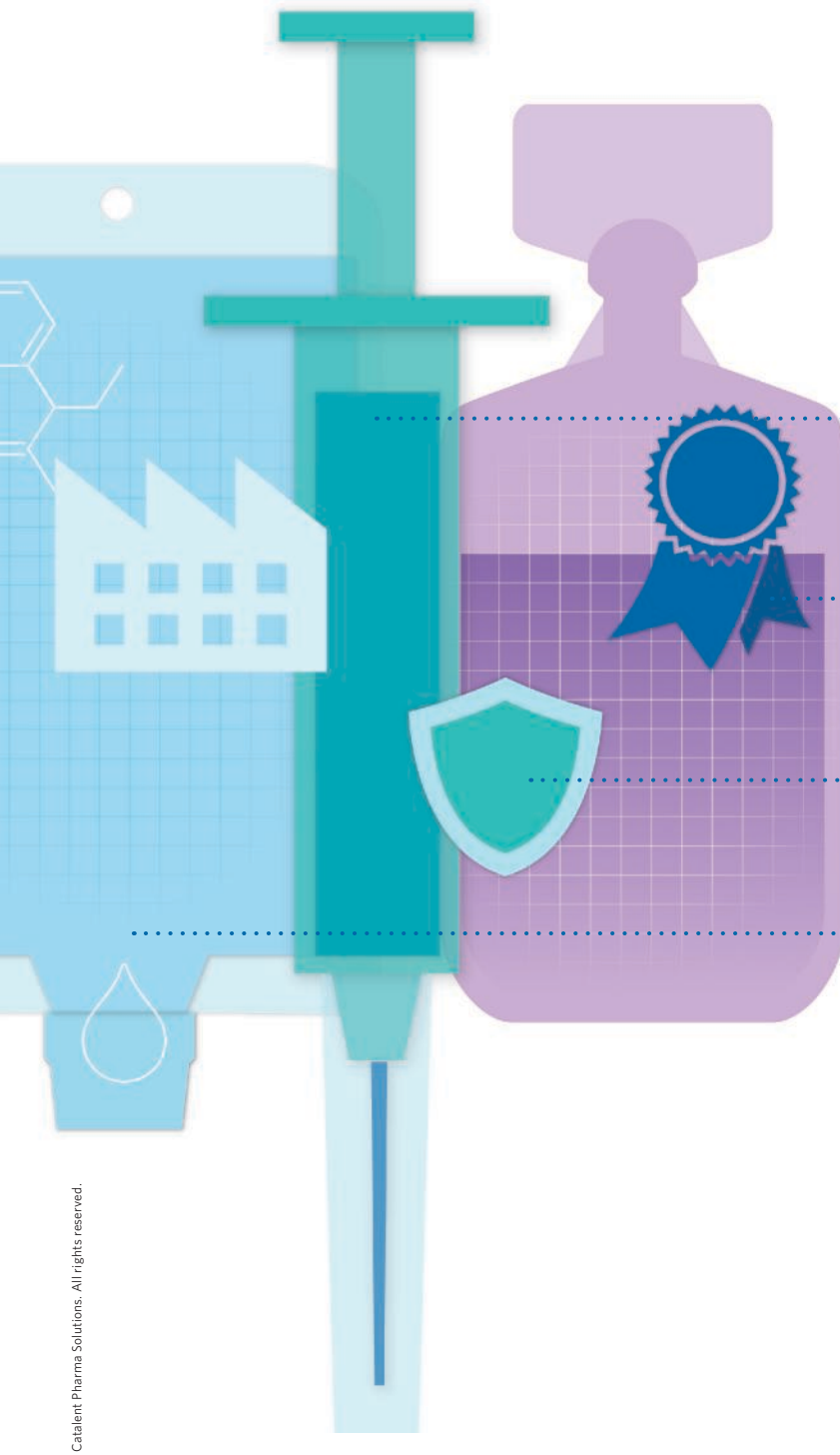

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