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Departments/Products

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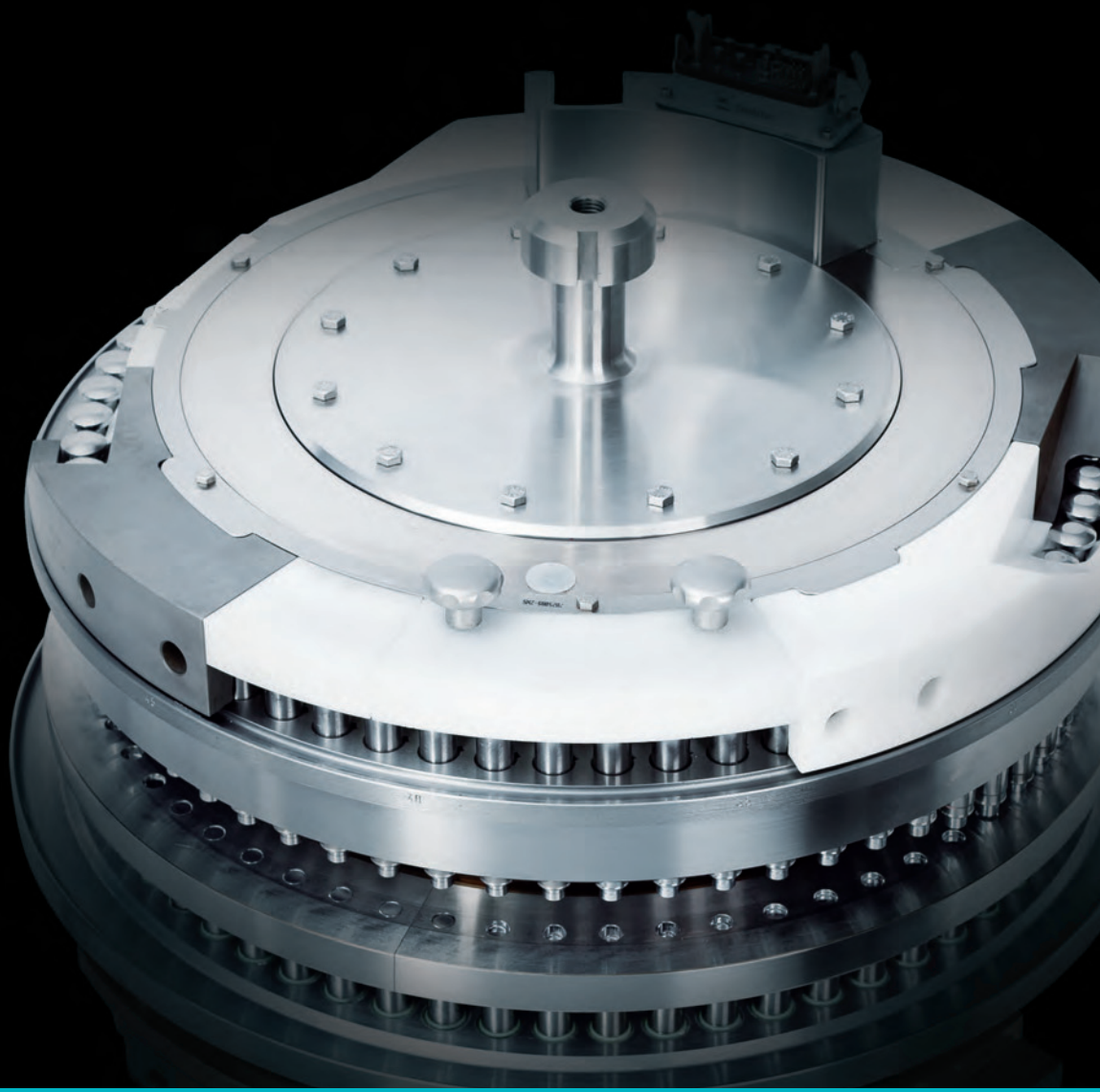

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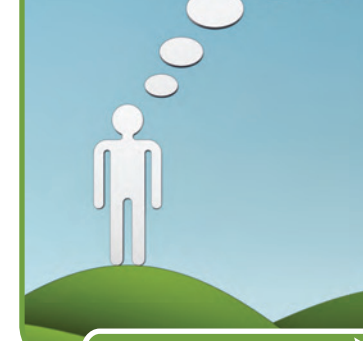

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The Truth About Drug Shortages

Angie Drakulich

Manufacturers willing to report the bad news about supply can help reverse the shortage trend.

At the beginning of each month, I get an automatic email notification from FDA noting the latest drug shortages that exist in the US market. As of early June, there were about 130 product types listed on FDA's drug-shortage webpage. Most of the affected products are cancer medications, anesthetics used for patients undergoing surgery, emergency medications, and intravenous electrolytes. Sterile injectables dominate the list and are prime targets for shortages because of limited production lines and capacity challenges, explains the FDA webpage. The reasons given for the various shortages include everything from manufacturing delays to increased market demand to material (API) shortage to product discontinuation.

FDA points out that shortage information is provided "voluntarily by manufacturers" and that the agency "cannot require firms to report the reason for shortage or duration of the shortage or any other information about shortages." This may soon change however. Earlier this year, FDA issued a draft guidance, *Notification to FDA of Issues that May Result in a Prescription Drug or Biological Product Shortage*. The guidance is meant to address growing concerns about drug shortages, which have tripled from 61 in 2005 to 178 in 2011, states the draft guidance. In 2011, FDA tracked over 250 drug shortages. These shortages can prevent patients from getting the crucial medications they need, when they need them. In addition, shortages can lead to larger problems. For example, in late May, FDA warned the public about a counterfeit version of Adderall being sold on the Internet—the counterfeit version contained the incorrect API. The drug just happens to be on the shortage list due to API supply issues.

Although the agency cannot do anything to stop drugs from being discontinued—that is the manufacturer's choice—it can do something about supply and quality problems that lead to shortages and about the way shortages are reported and tracked. A goal of the guidance is therefore to increase communication between industry and regulators in an effort to protect the public health. Reporting planned discontinuations of life-saving drug products to the authorities has been a requirement of manufacturers since about 1997 under Section 506C of the Food, Drug, and Cosmetic Act. However, the new draft guidance goes further by clarifying who has responsibility for such reporting: the "sole manufacturer," defined by the draft guidance as "the only applicant currently supplying the US market with the drug product" where drug product includes specific strength, dosage form, and route of administration. The draft guidance also redefines the term "discontinuance" to include "any interruption of manufacturing of a drug product described in paragraph (b)(3)(iii)(a) for sale in the United States that could lead to a potential disruption in supply of the drug product, whether the interruption is intended to be temporary or permanent."

In October 2011, FDA reminded manufacturers *via* letter of their mandatory reporting requirement and encouraging them to voluntarily report any disruptions in supply that could lead to a product shortage. That same month, President Obama ordered FDA to "use all available administrative tools to expand the Agency's efforts to combat the problem of drug shortages." The new draft guidance aims to carry out that order and to further enforce Section 506C. The draft document specifically calls out certain actions that may lead to a temporary or permanent drug supply problem, such as delays in acquiring active or inactive ingredients, equipment failures, and manufacturing shutdowns, whether for maintenance or routine matters. Manufacturers will need to notify FDA of these issues if they could lead to a disruption in supply. The agency also asks industry in the draft guidance to notify it on a voluntary basis (the above items would be mandatory with the final guidance) when certain problems could "reasonably" be expected to lead to a drug shortage or disruption (e.g., stability concerns, facility transfer, etc.)

I have high hopes for the guidance. In 2010, for example, 38 shortages were prevented because companies notified the agency of potential problems. Just as we tell our children, it's always best to tell the truth—even if it hurts a little to do so—because in the end, it's simply the right thing to do. **PT**

Comments on the FDA draft guidance were due at the end of May 2012. According to the FDA press office, 16 comments were submitted and a final guidance is expected to be issued promptly. In the meantime, companies and suppliers can send relevant shortage information to drugshortages@fda.hhs.gov.

Angie Drakulich is editorial director of *Pharmaceutical Technology*. Send your thoughts and story ideas to adrakulich@advanstar.com.

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Healthcare Reform is Given the Go-Ahead: Now What?

Jill Wechsler

No matter the upside or downside to the Affordable Care Act, there's work to be done.

The main result of the Supreme Court decision in late June to uphold the Affordable Care Act (ACA) is that it ends all the rampant speculation and uncertainty about the future shape of the US healthcare system. Now healthcare providers, insurers, medical products makers, and government agencies can move forward with the complex process of establishing new programs and policies to expand coverage to millions of Americans. Patients can expect more coverage options and improved access to care, including prescription drugs.

The much-anticipated ruling produced an audible sigh of relief from the healthcare industry, even those parties that would have preferred to see much of the program disappear. For biopharmaceutical and biotechnology companies, the decision means that FDA can continue to implement the new biosimilars program and that industry will continue to pay higher Medicaid rebates and provide discounts to Medicare patients who reach the Part D doughnut hole.

In return, some 33 million more people will gain help in paying for drugs and medical products over the next decade through health-insurance exchanges and expanded state Medicaid programs. It is this anticipated market increase that prompted the industry to support the Obama administration's healthcare reform initiative three years ago and agree to provide more than $80 billion in fees and rebates to support the program. Companies also have to pay hefty excise taxes, a requirement opposed by medical-device makers, who are pushing for repeal of a $30-billion tax on their sector over the decade. The decision also will encourage more comparative effectiveness research under the auspices of the Patient-Centered Outcomes Research Institute, which is authorized by the ACA.

For biopharma companies, the decision means that FDA can continue to implement the new biosimilars program.

Yet, biopharmaceutical companies and some providers continue to press for eliminating the Independent Payment Advisory Board (IPAB), which they predict will lead to price controls. At a recent seminar on biomedical innovation sponsored by the Brookings Institution, Amgen Chairman Kevin Shearer described IPAB as "a really bad idea" that could derail biotech product development. Jim Greenwood, president of the Biotechnology Industry Organization (BIO), said that IPAB "threatens patient access to needed cures and medical breakthroughs."

With regard to Medicaid, although the High Court declared the individual mandate constitutional, it curbed the requirement that states expand Medicaid eligibility or face a loss of federal Medicaid funds. The Justices supported the program expansion, but limited the penalty for states that choose not to comply. States that decide not to expand eligibility would lose only the additional payments for broader coverage, and not all federal Medicaid funding. It's not clear how states will respond to this more flexible option. Even if they decide on expansion, legal experts believe that the Medicaid decision has the potential of imposing more long-term limits on the growth of federal social welfare programs, and may end up having a significant impact on government initiatives and future court decisions. In addition, states face the enormous task of establishing insurance exchanges, overhauling health IT systems, and implementing a host of ACA provisions.

Overall, the decision to uphold the constitutionality of the ACA is a major political victory for the Obama administration. In ruling that the individual mandate is a legal tax and that individuals can decide to pay the tax instead of purchasing health insurance, Chief Justice John Roberts took a step that will intrigue legal scholars and Supreme Court experts for years. In rejecting the Commerce Clause as the basis for expanding health coverage, though, the ruling may place significant limits on future federal government expansion.

The future of healthcare in the US now depends on who controls the White House and Congress after the November elections. Republicans have pledged to dismantle Obamacare if they win in November, and health reform will be a prime campaign issue. Reform advocates won a major battle, but the war over healthcare will continue. **PT**

Jill Wechsler is a contributing editor to *Pharmaceutical Technology*.

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In the Field

Report from: Japan

Jane Wan

After a series of government reforms that are appealing to both domestic and foreign players, the Japanese pharma market is making a comeback.

In March 2012, Pfizer Japan, a subsidiary of Pfizer US, set up a Rare Disease Division with the objective of becoming a global leader in treating rare diseases. China's Beijing Genomics Institute (BGI) in the Yantian District of Shenzhen, formed BGI Japan in Kobe, in September 2011, to increase its range of partners and to conduct joint research with Japanese companies. Golden Biotechnology Corporation in Taipei, Taiwan, established a Tokyo-based subsidiary in April 2011 to push out its proprietary health supplements. And the list goes on.

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The well-established Japanese pharmaceutical market continues to attract extensive foreign interest and investment. Alan Thomas, director of business planning and analytics at IMS Japan K.K., says: "An increase in chronic disease, such as diabetes and cardiovascular related, and the number of treated patients within these diseases continues to see expanded access to pharmaceuticals. Additionally, an increase in specialty-related disease areas, such as oncology and osteoporosis, drives growth with increased use of biologics and specialty pharmaceuticals. With these emerging and expanding disease areas, the number of innovative treatment options available is also improving."

Japan's stagnating economy and aging population have urged the government to reshape healthcare policies that favor the entry of foreign firms. The agency has taken steps to shorten the drug-approval process and facilitate easy access to better treatment options. The median drug approval has fallen from 22 to 15 months in the past two years; and the approval time for products under priority review has dropped from 15 to 9 months.

The government is considering "a compassionate use" system that allows seriously ill patients to use drugs yet to be approved for use in Japan. This program is meant for patients who have not responded to standard treatments and where domestic options are unavailable. The government is also looking to allow health insurers to shoulder some of the costs incurred by patients under this system. Japan has spent time examining the sector's clinical trials and pricing as well, and under new initiatives, the increased acceptance and use of global clinical-trial data has reduced cost and sped timelines. The so-called "clinical triangle" comprising of China, Korea, and Japan, also helps to reduce development time in Japan because of the additional trial data available. In addition, the extension of Japan's "premium for development of new drugs and elimination of off-label use" is applicable to the National Health Insurance (NHI) price revisions established in April 2010. Under this system, manufacturers are encouraged to develop new drugs and provide additional information for existing ones when products are eligible for a lower NHI price revision.

Recently, the government shifted its focus to generic drugs with the goal of increasing market share to 30% by 2013 in a bid to address to the country's overburdened healthcare system. To dispel the common public perception that generic drugs are inferior, generic drugs and their active ingredients are placed under rigorous quality control. Generic-drug manufacturers are required to supply all of the strengths and dosage forms of the branded version. The Ministry of Health, Labor, and Welfare (MHLW) also requires manufacturers to supply strengths of the same dosage form as those of the branded products, and that the generic versions be a perfect match to the branded products.

Ranjith Gopinathan, program manager of life sciences and healthcare practice at Frost & Sullivan, adds, "Strongly backed by the government, the generics market is encouraged by initiatives such as relaxing registration procedures and providing incentives to doctors prescribing them over branded drugs."

Interestingly, foreign presence has reshaped the business strategies of domestic players. Jamie Davies, head of pharmaceuticals and healthcare at Business Monitor International, says, "Typically, Japanese pharmaceutical companies are conservative in nature and focus primarily on the domestic market and have limited exposure in less developed states. However, the dual effect of patent expiries and reduced research productivity has forced them to increasingly look abroad for sales growth. As a result, several are looking to emerging markets to generate new growth."

Japan's stagnating economy and aging population have urged policies that favor the entry of foreign firms.

Domestic companies have started to forge strong links with international firms and foreign markets. All the leading Japanese firms derive around 40% of their revenue from overseas markets, mainly the US, although exposure to emerging markets is increasing, adds Davies. In October 2010, Takeda Pharmaceutical in Tokyo announced plans to form alliances with Indian companies to sell its patented drugs and to offer basic business services.

The M&A quest has also gained momentum in Japan with Takeda's acquisition of Nycomed, based in Zurich, Switzerland, for $13.7 billion in September 2011. Takeda Farmacêutica Brasil has signed an agreement to acquire Multilab Indústria e Comércio de Produtos Farmacêuticos, based in Rio Grande do Sul, Brazil, by the end of the second quarter of 2012.

Of course, there are exceptions. Recently, Eisai, based in Tokyo, has shifted its focus back to East Asia, citing the region's enormous potential, especially now that the Japanese market is becoming attractive again thanks to government initiatives. Likewise, Sawai Pharmaceutical in Osaka is concentrating on the Japanese market and exploring partnerships with larger pharmaceutical companies to expand its therapeutic range.

Thomas adds, "From a portfolio perspective, Japanese pharmaceutical companies will put their focus on speciality pharma, oncology, and biological platforms. This acquisition activity will gain momentum as a strategy for market entry and portfolio expansion." Although domestic firms control 66% of the Japanese pharmaceutical market share, the market remains attractive to foreign big players for its lower risk and exposure compared with other markets. In fact, a Bloomberg source indicates that the prominent companies are doing quite well. Pfizer grew Japanese sales to $7.3 billion last year and GlaxoSmithKline figures were up by 28% in the same year. Large-scale companies are well-positioned due to their strong late-stage pipelines and aggressive launch objectives to continue to grow over the next two to three years. On the other hand, smaller-scale players with no presence in Japan may have to opt for out-licensing or partnering to maintain growth. *Jane Wan is a freelancer writer based in Singapore*

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Technology Fights Back

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Cautionary Tales from the Files of "Control," a Senior Compliance Officer

Meticulous system configuration can prevent the machines from taking over your product batches.

Gold standard

"We used a single-use specialized nanofilter for decades," began our GMP Agent-In-Place. "We were an innovator in our particular use, and during the FDA-approval process we had to develop a unique integrity test for the filter. Our supplier noted the filter was difficult to make and experienced many rejects. Some filters failed during integrity testing. We were the last customer they had for this specific nanofilter as they had convinced their other customer to change over to a new filter. The suggested replacement for our older filter was $700. The filter was a new technology filter priced at $5000—still single-use. However, we did not make the replacement filter pass qualification testing in our process. Because the supplier was insistent on canceling production, we looked at other suppliers. We finally found a filter that would fit in our process (at $3000 each). However, the integrity test required use of suspended and standardized gold particles which added several thousand dollars to each use. People wonder why pharmaceuticals cost so much, well, our costs went up a half-million dollars a year because the supplier discontinued its product."

Caustic quality

"When your bioburden trend goes out of control, you need to take action," our GMP Agent-In-Place noted. "We had a nonsterile process in which the bioburden was increasing, and the manufacturing staff was not finding the source. The Quality team spent time on the manufacturing floor during all shifts to watch the activities. While we were there, the bioburden went back to historic levels, although no new activities had been instituted. It was only when the investigation team started reviewing equipment log books that they realize that during the bioburden excursions, the standard operating procedure that required caustic soak of the vessels had been forgotten."

Unfortunately, there was a bug in the configuration of the live system.

Confusing configuration

"We had just switched from distributing our product directly from the manufacturing site to using a third-party logistics (3PL) partner," said our stunned GMP Agent-In-Place. "Our release computer system was linked to the 3PL's computer system, which used a two-step release process. Step one involved the manufacturing site release information and step two focused on the transit temperature review. When these requirements were met, the computer system would automatically release the batch. After our usual validation testing and approval, we turned the process on. Unfortunately, there was a bug in the configuration of the live system and some batches were released without the proper prerequisites. Luckily, we were carefully watching the system during the first couple of days from two different sites and caught the issue before unreleased product was distributed. We quickly tweaked the configuration and now the system works as desired. Lesson learned: the test system isn't always completely identical as the live system."

Spring cleaning

"We had two manufacturing sites located in the same city," said our GMP Agent-In-Place as he began his complaint. "The sites shared the Quality department. Also, the supplier-qualification process included testing and auditing. Both sites performed extensive remodeling, which required several automated cleaning processes, and each site had new procedures for cleaning and disinfection. The projects were run by separate groups, so each picked its own new clean-in-place agents and disinfectants. Each group needed extensive laboratory characterization and test development as well as numerous supplier audits. And each team insisted that its different equipment vendors 'required' these new and unique materials. Yes, we did get all the necessary laboratory work completed and did successfully perform the audits. But a little coordination up front would have saved several hundred-thousand dollars." **PT**

Pharmaceutical Technology's monthly "Agent-in-Place" column distills true-life cautionary tales from the files of Control, a senior compliance officer. If you have a story to share, please email it to Control at AgentinPlace@advanstar.com. We won't use any names, but if we do use your experience in the column, you'll receive a Pharmaceutical Technology t-shirt.

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Editors' Picks of Pharmaceutical Science & Technology Innovations

Faster testing can improve efficiency of both the laboratory and the overall manufacturing process. This month's featured products are designed to be easier to use and to produce results faster while maintaining accuracy. A total organic carbon (TOC) analyzer from Swan Analytical measures TOC in pure and ultrapure water. A direct sample analysis system from Perkin Elmer eliminates sample preparation steps. A light-weight, portable particle counter from Kanomax has an increased flow rate.

AxION Direct Sample Analyzer and AxION TOF Mass Spectrometer System
PerkinElmer
www.perkinelmer.com

Total organic carbon analyzer tests pharmaceutical water

Swan Analytical's AMI Line total organic carbon (TOC) analyzer is designed for continuous, accurate measurement of TOC in pure and ultrapure water in the pharmaceutical industry. The instrument has a range of 0.1–1000 ppb TOC and a resolution of +/– O.1 ppb. TOC is measured using UV oxidation and differential conductivity detection, with results in less than two minutes. The analyzer is designed for ease of performing a system suitability test (SST). Standard sucrose or benzoquinone solutions are automatically added, and grab samples can be taken by pushing a button. In addition, automatic sensor verification uses less expensive, durable, concentrated standards that are automatically diluted, which allows the user to verify the accuracy of the measurement without performing a SST. The analyzer's electronic drift stabilization provides long term, stable analysis results.

AMI Line TOC analyzer
Swan Analytical
www.swan-analytical-usa.com

System reduces sample preparation for mass spectrometry

PerkinElmer's AxION Direct Sample Analysis (DSA) system is designed to introduce liquid, solid, and gas samples directly to PerkinElmer's AxION Time-of-Flight (TOF) mass spectrometer. The DSA system eliminates sample preparation steps and removes the need for front-end gas or liquid chromatography separation because samples can be directly introduced to the mass spectrometer. Using the DSA system reduces sample preparation time from a typical 25 min. down to 25 s. The integrated DSA system is entirely enclosed to prevent atmospheric contamination of samples and fully automated for fast data acquisition.

Portable particle counter is easy to transport

The Kanomax Model 3910 50LPM Portable Particle Counter can simultaneously measure six particle sizes in tasks such as cleanroom verification, clean bench verification, filter testing, and facility certification. The model is designed to be small and light so that it is easy to transport and manage in the field. This model has an increased, 50 L/min flow rate, which increases testing speed. The unit has a stainless steel enclosure and is compliant with ISO 21501-4 and 21 *CFR* Part 11. The instrument features an intuitive, LCD touch screen and preprogrammed standards, and stores up to 10,000 measurements. An optional Climomaster probe measures air velocity, temperature, and humidity.

Model 3910 50LPM
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- Opening Keynote Address by **W. Bradley Fain**, PhD, Georgia Tech Research Institute (Sponsored by West Pharmaceuticals) on ***Addressing the Needs of the Patient***
- Numerous plenary, concurrent, interest group and breakfast sessions
- Closing plenary session on ***Global Market Assessments and Panel Discussion*** featuring:
  - **Brigitte Reutter-Haerle**, *Vetter Pharma International*
  - **Ian Thompson**, *Ypsomed*
  - **Sheldon Moberg**, *Amgen, Inc.*
  - **Kingman Ng**, PhD, *Novartis Vaccines & Diagnostics*
  - **Thomas Schoenknecht**, PhD, *SCHOTT*
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  - **FDA Representatives Invited**

Immediately following the conference, PDA's Training and Research Institute (PDA TRI) will be hosting three courses onsite October 18-19.

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FDA User-Fee Legislation Sets Stage for Manufacturing Changes

Jill Wechsler

Import controls and risk strategies aim to promote quality and spur new drug development.

There was much celebrating on Capitol Hill in late June, as leading legislators reached across party lines to approve the Food and Drug Administration Safety and Innovation Act (FDASIA) in record speed. The bill (S. 3187) enables FDA to collect approximately $6 billion in fees over the next five years from pharmaceutical and medical device companies. These fees are crucial to maintaining an efficient prescription drug regulatory system.

At the same time, the Supreme Court upheld the constitutionality of the Affordable Care Act. The decision ended speculation that FDA might lose authority to establish a pathway for developing new biosimilars [see Roundup].

Now the hard work begins to implement new policies and prepare the multiple guidance documents and reports required by FDASIA. As with most 300-page bills, the FDA legislation has something for everyone: patient advocates gained added incentives for developing crucial medicines; providers applauded policies to curb drug shortages; and manufacturers may benefit from speedier approvals and stiffer penalties for counterfeiters.

The basic user-fee program for drugs and biologics hashed out by manufacturers and FDA officials over the previous 18 months remained intact during the legislative process. Generic-drug makers agreed to pay almost $300 million annually to accelerate approvals, clear up an immense application backlog, and support timely inspections of foreign manufacturers. In addition, firms developing new biosimilars agreed to provide upfront fees to cover some of FDA's cost in providing guidance to sponsors, a program expected to raise $128 million over five years.

Manufacturers face multiple state tracking requirements.

Supply chain security

As the analysts and lawyers continue to pore over the fine print in FDASIA, some questioned whether policymakers should have taken more time to resolve some contentious issues, such as how to establish a national track-and-trace system for prescription drugs. Policymakers were stalemated by industry's support for tracking based on lot number, instead of individual vials and bottles, as FDA preferred. Manufacturers thus face multiple state tracking requirements, starting with a California law that goes into effect in 2015.

Still, the final law contains a wealth of provisions designed to help FDA detect and block adulterated and illegal medical products. All drug manufacturers and foreign suppliers have to register with FDA, using a unique facility identifier. Importers face a number of specific registration requirements, including electronic information submission. FDA can block the import of products from manufacturers that deny access to inspectors or fail to submit requested records. FDA has also been given authority to detain adulterated products at the border instead of having to send them back to the shipper, and in some situations to destroy violative imports.

Manufacturers are required to notify FDA if a drug may be stolen or counterfeited, and intentional adulteration for economic gain carries stiff penalties, including jail time. The consequences are even more serious for anyone who intentionally traffics in counterfeit drugs.

An important change overrides the established, but long unworkable two-year plant inspection requirement and permits FDA to inspect drug-manufacturing facilities on a schedule that reflects risk factors. Another innovative provision specifies that meeting cGMPs requires manufacturers to implement quality management systems and assure the quality of raw materials. FDA may share trade secret information with trusted regulatory counterparts and gains leeway to consider inspection information from such regulators in evaluating the risk level of an establishment. The bill also specifies that US law governing drugs and medical products may be applied to extraterritorial violations, such as economically motivated adulteration of products like heparin.

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CRODA

Hot-Topic Roundup

Supreme Court upholds Obamacare

Pharmaceutical and biotech manufacturers can expect FDA to develop a pathway for testing and approving biosimilars as the Obama administration implements the multiple provisions of the Affordable Care Act following the landmark Supreme Court ruling. Industry also will continue paying higher Medicaid drug rebates and hefty excise taxes to the Treasury, along with discounts on drugs prescribed to Medicare patients in the "coverage gap" (see PharmTech Talk, page 14).

No overtime for sales reps

Another important Supreme Court decision for pharmaceutical companies rejected demands from sales representatives for overtime pay. A narrow conservative majority ruled that the detailers employed by GlaxoSmithKline are not protected by the Fair Labor Standards Act (FLSA) because they are "outside salesmen" that do not actually sell products, but provide information to physicians designed to stimulate prescribing. The ruling is regarded as a rebuke to the Department of Labor and the Obama administration, and it is expected to halt the wave of lawsuits filed against manufacturers over recent years. But the decision may be good for sales representatives, according to some analysts, because pharmaceutical companies otherwise might lay off even more detailers than they already have.

FDA promotes supply-chain pilot

Just as Congress approved FDA user-fee legislation without any provision for establishing a national drug track-and-trace system, the agency indicated it was moving forward with a long-planned pilot to test ways to ensure the quality and integrity of imported pharmaceutical ingredients and finished products. The Secure Supply Chain Pilot Program was originally proposed in 2009 but generated concerns about excessive red tape and oversight. Now FDA has revised the program and is seeking final approval from the Office of Management and Budget to move forward. FDA's plan is to select up to 100 manufacturers and importers that each submit information on how five drugs will be imported into the US. Applicants must maintain records documenting the product's movement through their secure supply chain, meet customs requirements to guard against terrorism, and demonstrate that they comply with good importer practices proposed by FDA.

Regulating apps

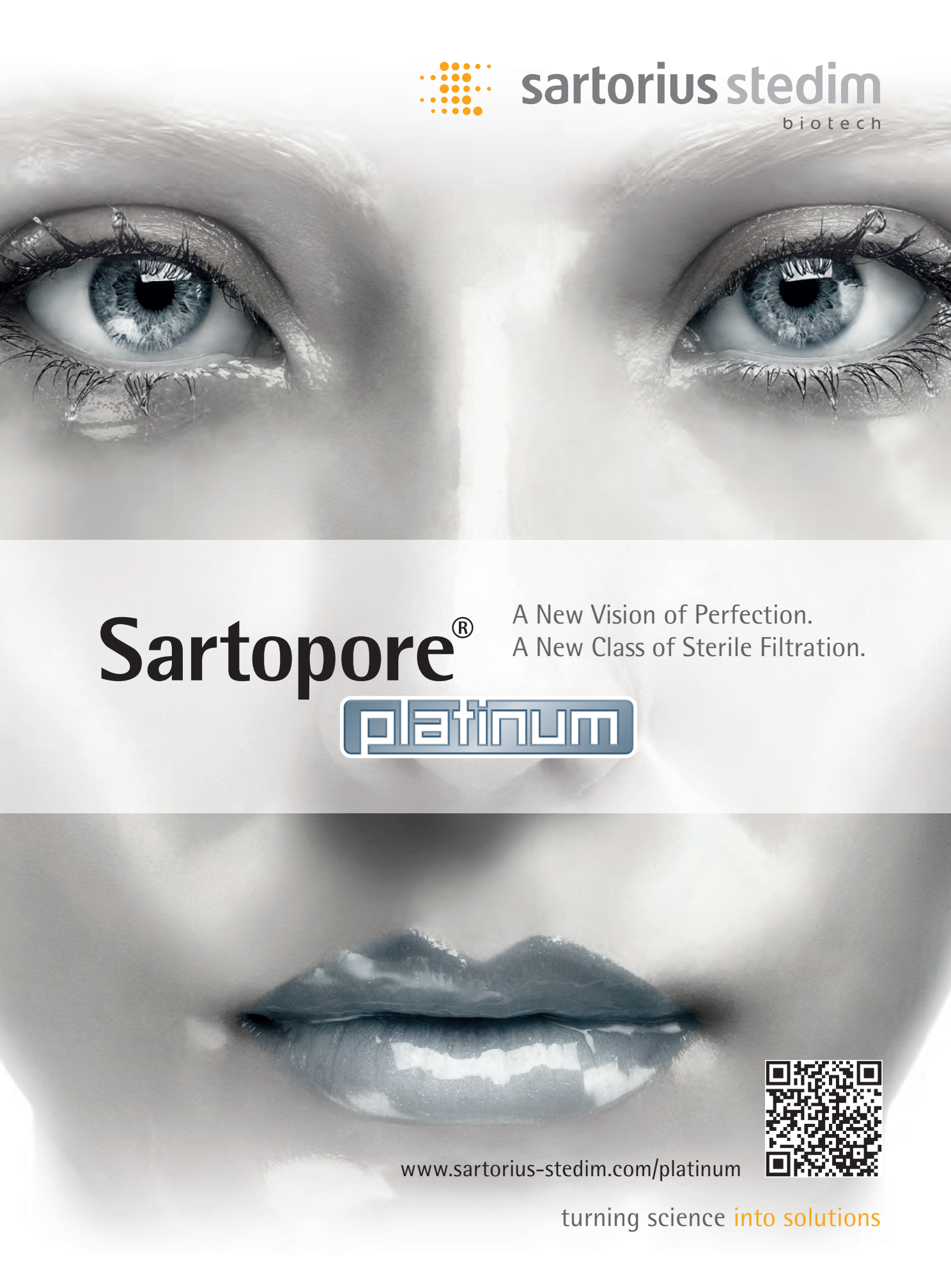
A fairly obscure provision in the FDA Safety and Innovation Act seeks to clarify how FDA may—or may not—regulate medical applications for smart phones and other computer devices, a hot issue with manufacturers and health authorities. The final bill stops short of prohibiting FDA from finalizing a draft guidance document issued last year that proposed agency regulation of software that links to a device, but not low-risk applications such as calorie counters. Consequently, FDA officials are expected to hold off on drafting a final guidance until it forms a working group, as required by FDASIA, to quickly (in 18 months) develop a strategy for an "appropriate, risk-based regulatory framework" on health IT "that promotes innovation, protects patient safety and avoids regulatory duplication." FDA will consult with the National Coordinator for Health Information Technology and the Federal Communications Commission and include manufacturers, payers, venture capitalists, IT vendors, patients, providers, and others in the working group.

The compromise measure reflects concerns of software and medical device companies that FDA will over-regulate this budding industry, squashing innovation and promising health technology. There already are some 40,000 medical apps, some developed by pharmaceutical manufacturers looking to enhance patient use of treatments for diabetes and other medical conditions and to help manage clinical trials. FDA regulates medical software that controls x-ray machines, infusion pumps, and certain implants and recently approved a medical app that displays radiological images. Some software developers support FDA regulation to gain more predictability in market requirements, despite the cost and time of compliance.

Biomedical innovation in trouble?

The time and cost of developing new drugs are rising, venture capitalists make no return on investments in biopharma R&D, and other countries are boosting support in this area while US policymakers propose funding cuts for the National Institutes of Health (NIH). Experts painted this bleak picture of the "state of biomedical innovation" at a June seminar sponsored by the Brookings Institution. There is a "relentless decline" in biopharma R&D productivity, as measured by the number of new drugs approved compared with spending on R&D, pointed out Jonathan Leff of Warburg Pincus. NIH Director Francis Collins warned that the US faces a decline in its scientific leadership and competitiveness as visionary scientists find research funding increasingly difficult to obtain. FDA Commissioner Margaret Hamburg cited the impact that reimbursement and immigration policy have on innovation, and that FDA strives to serve as a gateway, and not a barrier, to advancing new product development.

Amgen Chairman Kevin Shearer sounded a more optimistic tone, noting that the US biotech industry continues to "dominate the world," and that no other country "is even close" to the US in providing the financial support and scientific infrastructure for biopharmaceutical innovation. If you develop an innovative medicine in America "you'll be rewarded," he noted. The main strategy for the research community, said Shearer, is to continue investing in NIH, which he termed "a national treasure," and to "leave FDA officials alone."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To curb shortages of critical drugs and biologics, the law extends reporting requirements for manufacturers anticipating short supply situations. FDA gains clear leeway to expedite establishment inspections and application reviews to help mitigate or prevent a shortage, along with requirements to issue an annual report on drug shortages and to maintain a drug-shortage list that will help patients and providers keep informed of supply problems. The Drug Enforcement Administration has to provide timely approvals or denials of requests to increase quotas of controlled substances when needed to address a drug shortage. And a new Health and Human Services (HHS) task force will examine ways to enhance the federal response to shortages and create a strategic plan to address these problems.

Accepting risk

This fifth version of the Prescription Drug User Fee Act (PDUFAV) offers additional assistance for research sponsors and greater transparency in the application review process to complete more first-cycle reviews. Patient advocates played a prominent role in pressing for provisions to accelerate FDA approval of new treatments for serious and life-threatening conditions, along with articulation of an FDA risk-benefit framework to clarify that new drugs are never absolutely safe, and that patients accept a certain amount of risk in using new treatments.

FDA may share trade secret information with trusted regulatory counterparts

Specific provisions provide expedited review of fast-track products and clarification of evidence and endpoints to support accelerated approval of drugs for serious or life-threatening conditions. Grants for developing orphan-drug products will continue, and revised conflict-of-interest rules will make it easier to bring in knowledgeable experts to serve on advisory committees, especially those committees dealing with rare diseases.

Infectious disease experts gained incentives for developing new antibiotics: an added five years exclusivity will apply to specific "qualified infectious disease products," which FDA has to define and list.

Other provisions encourage development of new formulations and expanding labels for drugs for children. The Best Pharmaceuticals for Children Act and the Pediatric Research Equity Act were made permanent, instead of requiring reauthorization every five years. A new pilot program will test whether an offer of priority review vouchers, which can be redeemed for a speedy FDA review of another product, will accelerate development of new therapies for rare childhood diseases.

A less-noticed but important provision requires electronic submission of applications for drugs, once FDA establishes policies and standards for doing so. In this part of the bill, the legislators take the unusual step of permitting FDA guidance to set requirements, a strategy that aims to move this policy forward without a lengthy rulemaking process. And the final bill aims to reduce duplicative clinical studies by encouraging FDA to accept foreign clinical trial data to support new drug applications.

FDASIA also makes it easier for manufacturers to make minor modifications in risk evaluation and mitigation strategy (REMS) programs. Generic-drug makers, however, lost out in their campaign to prevent brand firms from using REMS to block access to products needed to test and develop new generic competitors, an issue that could affect biosimilar development down the road. However, other changes in generic exclusivity policy and procedures for handling citizens' petitions promise to enhance access to generic drugs.

Policymakers sought to add restrictions on the prescribing and sale of opioid painkillers to rein in the rampant abuse of these prescription products, but pharmacists objected strenuously. So instead, FDA will hold a public meeting on the need to reschedule hydrocodone and seek ways to exchange prescribing information across state lines to help pharmacists detect multiple painkiller prescriptions. These discussion are likely to address FDA's long-awaited REMS for extended-release opioids, which was issued just after FDASIA was finalized. The REMS stops short of mandating education for opioid prescribers, opening the door to further debate and legislative proposals on controlling these drugs. **PT**

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Small Changes, System-Wide Impact

Simon Chalk and Steve Jones

A look at elastomer changeout times shows how industry knowledge improves 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 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. 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). 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 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. **PT**

Simon Chalk (simon@biophorum.com) and **Steve Jones** are both directors of the BioPhorum Operations Group.

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Quality Control Advances

Hallie Forcinio

Highly automated and sensitive quality-control equipment quickly identifies product faults.

Quality control requires constant attention on pharmaceutical packaging lines, but it doesn't have to cause sleepless nights for operators and managers. Today, faster and more sensitive quality-control equipment provides continuous online vigilance. Data-collection capabilities are more robust too, which increases automation of record-keeping and validation. Vendors also are providing tools to help match quality-control systems to applications. Quality-control machines, introduced in the past year or so, are indicative of the technology available today and include systems for visual inspection, leak detection/seal integrity confirmation, checkweighing, and contaminant detection.

Visual-inspection systems

Visual-inspection systems, such as vision sensors, smart cameras, and camera-based vision systems, confirm the presence and position of caps, lids, and labels and check for particulates, label accuracy, and surface imperfections.

For the most demanding applications, full-scale machine-vision systems provide the highest level of programming flexibility. Although machine-vision systems are still the most complex to set up and configure, software and operator interfaces streamline configuration and simplify operation.

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In the mid-range of functionality and ease of use, smart cameras combine a camera with onboard intelligence and an array of software tools that offer considerable flexibility for application programming.

The simplest and easiest to implement system, the vision sensor, also combines a camera with onboard intelligence and is optimized for optical-inspection tasks. A vision sensor can be taught to compare a captured image to a good sample and/or check for specific defects. Its capabilities are sufficient for many packaging-line inspection tasks (1).

Software is designed to be intuitive even for users who are not vision experts, said Jim Anderson, product manager for machine vision at SICK, in a company publication (1) (vision sensors, smart cameras, vision systems, SICK).

For pharmaceutical packaging applications, one robot-supported inspection machine handles almost any cylindrical container with a volume between 1 mL and 100 mL, including vials, syringes, ampuls, cartridges, cylindrical blow–fill–seal containers, and inhalers. The six-axis robot arm moves up to 15 containers per minute through three machine-vision inspection stations equipped with different camera, lighting, and container positioning options. In some cases, more than one inspection is performed at a single station. The system can check for the following: particles from a bottom or side view; proper cap application; dirt or cracks at the shoulder of the container; scratches, cracks, or chips on the neck, shoulder, or sidewall; cracks at the heel; flaws on the bottom of the container or heavy particles in suspension; and particle or cosmetic defects. The compact system is compatible with isolator enclosures and particularly well-suited for toxic or highly potent products (Seidenader RIM inspector with robot arm from Stäubli Group, Körber Medipack).

Another multiple-camera, machine-vision system examines tablets from six angles to confirm surface quality. Laser-slit lighting and three-dimensional images improve identification of chips and embossing flaws, while color cameras and filters detect subtle color variations. Simulation modes shorten set-up time, and fewer, lighter change parts reduce changeover time. The system runs up to about 5800 tablets per min (Viswill TVIS-EX3-CD visual inspection system for tablets, Daiichi Jitsugyo America).

A print quality inspection and barcode verifier for thermal and thermal-transfer printed labels performs a variety of inspections. Functions include master-to-label comparison (i.e., blemish detection), one- and two-dimensional barcode verification and validation, optical character recognition, optical character verification, field matching, and number/data validation. Additionally, the software includes automatic setup for quick label and field identification, job retrieval for recall of previous runs, and a robust alarm matrix for user-defined input/output interaction with peripheral devices. The rugged design of

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the read head and mounting plate simplify integration with thermal label printers and other slow-speed roll printing applications. The system is 21 *CFR* Part 11 compliant-ready, offering multiple security levels and comprehensive data management and reporting options (LVS 7500 inspection system, Label Vision Systems).

Leak detection/seal integrity

A high-speed, vacuum-based system provides 100% inspection of prefilled syringes for leaks at up to 600 syringes per min. The patented system positions the syringe so its entire surface can be checked without altering the position of the stopper or affecting the product. (Wilcomat R 36 MC/LFC high-speed leak tester, Wilco AG).

An inspection system based on infrared technology confirms seal integrity in flexible packaging and between thermoformed trays and lidstock (see **Figure 1**). A high-definition infrared camera captures an image of each seal immediately after sealing. Software analyzes the image, detects any abnormality in the seal, and rejects leakers. The equipment also monitors sealer function and can provide an alert if maintenance is needed (infrared seal inspector, Qipack BVBA).

High-voltage leak detection (HVLD) finds flaws in prefilled syringes, liquid-filled vials, blow–fill–seal containers, ampuls, and liquid-filled pouches. The off-line laboratory instrument nondestructively tests container/closure integrity and locates pinholes, microcracks, and other defects as small as 1 micron. Seamless migration to production-scale systems simplifies validation of 100% inline testing (Nikka Densok E-Scan 625 HVLD micro leak detection system, PTI Inspection Systems).

Checkweighing

Checkweighing improves product quality, meets regulatory requirements, and reduces production costs, according to a downloadable guide that helps drug packagers establish a checkweighing program and covers checkweigher design features, equipment accuracy and statistical process control (2). The document also defines operating goals, total cost of ownership, and metrological regulations and guidelines while supporting installation, verification, and limit setting to maximize efficiency and minimize costs (*Principles of Checkweighing Guide*, Mettler-Toledo Hi-Speed).

A family of mid-range, servo-driven checkweighers measures up to 7500 g at 250 per min and features a touch-screen operator interface, a 100-recipe memory, four password-protected user levels, validation support, and an extended event log. Product transport belt changes require no tools, and a variety of reject devices are offered. High ground clearance simplifies cleaning (HC-M-WD washdown IP69K checkweigher, HC-M-VA stainless steel design IP65 checkweigher, and HC-M-MDi checkweigher/metal detector combination, OCS Checkweighers).

Contaminant detection

Today's metal detectors can locate smaller metal fragments. One system detects ferrous fragments as small as 0.25 mm with a 95 × 22 mm head. The machine is capable of checking up to 30,000 solid dosage forms per min and successfully locating metal fragments in difficult-to-inspect liquid gels or iron-containing tablets by filtering out the signal emitted by the product itself. A slightly less sensitive 95 × 38 mm head also is available (Insight PH pharmaceutical metal detector, Lock Inspection Systems).

Contaminant-detection systems with X-ray technology can "see" a wide range of foreign objects. One family of advanced X-ray detectors offers mixed product and multilane inspection and count, seal, and weight confirmation. Other features include toolless disassembly for cleaning, compact 60-in overall length, low-profile design, and auto-learn mode for easy setup. One model is shown in **Figure 2** (E-Z Tec XR-Pack X-Ray detector, Eriez). One of the latest models checks upright packages and containers from the side with a side-shoot beam rather than the up-shoot beam that is standard in other models in the group (E-Z Tec XR-SS X-ray detector, Eriez).

Another X-ray system detects subvisual foreign particles in lyo cakes and suspensions in vials, ampuls, or syringes with a substantially lower false reject rate than traditional camera-based inspection systems. Detectable particle sizes include 20 microns for metal, 50 microns for glass and 90–100 microns for plastic or rubber. Capable of checking 200–400 products per min, the inline or standalone X-ray system can be integrated with modules devoted to headspace analysis and near infrared-based lyo cake moisture detection. Bubbles, which can be problematic for some inspection systems, are virtually invisible to the X-ray beam, which also can confirm proper needle alignment and check for missing stopper material or splintered glass, defects that would ordinarily be concealed by the crimp cap (Wilcomat X-Ray particle detector, Wilco AG).

Figure 1. A seal inspector is based on infrared technology (infrared seal inspector, Qipack).

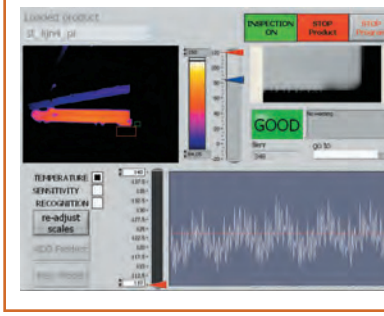

Figure 2. An X-ray detector looks for foreign objects and checks package integrity (E-Z Tec XR-Pack X-ray detector, Eriez).

References

1. J. Anderson, *Easily Solve Three Common Quality Control Problems in Packaging with Vision Sensors*, (SICK, Minneapolis, MN, 2012), p. 2.
2. Mettler-Toledo, *Principles of Checkweighing* (Mettler-Toledo, Columbus, OH, 2012). **PT**

TOP IMAGE COURTESY OF ERIEZ AND QIPACK & BOTTOM IMAGE COURTESY OF ERIEZ

Atypical Visible Particles (Black Specks): Approaches for Manufacturers and Users

LIVE WEBCAST: Thursday, September 13, 2012 at 11:00 AM EST

Register free at www.pharmtech.com/atypical

EVENT OVERVIEW

The presence of atypical visible particles (AVPs), also referred to as off-colored or black specks, affects both manufacturers and users regarding standard expectations for addressing AVPs and decisions about raw material acceptance criteria. The International Pharmaceutical Excipients Council (IPEC) is developing a guideline on how to measure and properly assess the significance of atypical visible particles.

This webinar will provide an industry-wide discussion of key challenges, best practices, and approaches for handling and responding to atypical visible particles from both a manufacturer and user perspective. Input from these discussions will be considered in the development of the IPEC guideline.

Who Should Attend:

- All makers and users of bulk pharmaceutical ingredients, especially those engaged in QC, QA, Regulatory, Manufacturing, and Purchasing.

Presented by

Pharmaceutical Technology

IPEC AMERICAS

Key Learning Objectives:

- To gain an understanding of the potential for Atypical Visible Particles to occur in bulk manufacturing.
- To explore the acceptability of discolored particles.
- To learn about IPEC's future guideline for Atypical Visible Particles.

Presenters

Ann van Meter
Lead Quality Manager, Dow Wolff Cellulosics;
Chair, IPEC GMP Committee;
Chair, IPEC Atypical
Visible Particles Working Group

Dave Bonilla
Regional Director of QA/QC Americas,
Colorcon

Chris Moreton
Vice-President, Pharmaceutical Sciences,
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Member, IPEC Expert Committees

Moderator:

Angie Drakulich
Editorial Director
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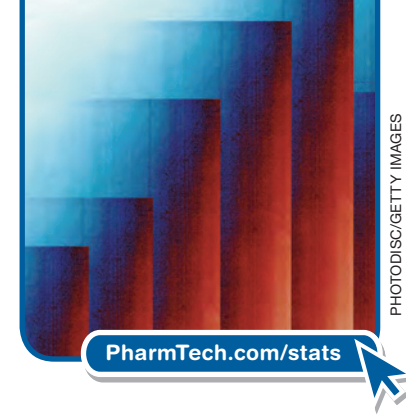
For questions contact Sara Barschdorf at sbarschdorf@advanstar.com



PHOTODISC/GETTY IMAGES

A Statistical Review of ICH Q10 *Pharmaceutical Quality System*

Lynn D. Torbeck

Applying the recommendations of ICH Q10 to statistical analysis can help prevent product recalls.

The International Conference on Harmonization ICH Q10 guideline, *Pharmaceutical Quality System*, and its two companion guidelines Q8 *Pharmaceutical Development* and Q9 *Quality Risk Management*, have been readily accepted if not fully implemented by the pharmaceutical industry over the past few years (1–3). Discussions of the statistical implications of Q8 and Q9 have appeared since theguidelines were harmonized (4). Little has been said, however, about the statistical content of the Q10 model, probably because it is perceived to be focused only on the management of the quality system. There are many Q10 recommendations that affect statistical issues facing the pharmaceutical industry, however, the guideline states that it is not "intended to create any new expectations beyond current regulatory requirements" (1).

Although no new statistics or sampling plans are explicitly required by Q10, it goes without saying that current regulatory requirements are, in fact, mandatory. In addition, cGMPs continue to improve over time and according to Q10, "Implementation of ICH Q10 throughout the product lifecycle should facilitate innovation and continual improvement and strengthen the link between pharmaceutical development and manufacturing activities" (1). That link should include the results of statistically designed experiments and related statistical and risk analysis.

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While not explicitly requesting these approaches, ICH clearly implies that companies need to be proactive when it comes to corrective and preventive action (CAPA) programs. In today's environment, it is not sufficient to be reactive alone when problems occur. The Quality department must routinely seek out potential problems and prevent them before they result in rejects or recalls. For example, Q10 notes that companies should "Establish and Maintain a State of Control. To develop and use effective monitoring and control systems for process performance and product quality, thereby providing assurance of continued suitability and capability of processes" (1).

Having control over one's product and process is not a new expectation, although there is still confusion as to what a proper "state of control" means (4). It is not enough to ask for a state of control; the industry must provide and define additional modifiers. There are several ways in which a process can be in a state of control or, conversely, in a "state of out of control."

A process can be in control, for instance, for financial and accounting, for regulatory compliance, and for organizational and managerial control. These forms of control are usually assumed to be in place. There are two other states of control that are germane to statistics: engineering and statistical.

A process is said to be in a state of engineering control when the process can be changed and adjusted using control knobs and/or by setting the critical process parameters (independent variables) that affect the dependent responses (5). When in control, the product always meets its specifications even if inconsistent and erratic. Time plots with specification lines are used to monitor the process. A process is said to be out of engineering control when it fails to meet its specifications.

A process is said to be in a state of statistical control when the process has been designed, developed, and adjusted to produce product that, while still containing some variability in the critical quality attributes (dependent variables), is predictable in that variability over time. Statistical control charts are used to monitor the process. A process is said to be out of statistical control when it fails one or more of the eight Western Electric control chart rules (6). As Q10 notes, "The pharmaceutical quality system should include the following elements, process performance and product quality monitoring, corrective and preventive action, change management, and management review" (1).

Product quality monitoring can be interpreted as trending the critical quality attributes. Again, proactive CAPA is preferred to reactive CAPA. As Q10 highlights: "Advocate continual improvement" (1). This continual improvement should include proactive variability reduction.

Also recommended in Q10 is: "… a written agreement between the contract giver and contract acceptor." This agreement should include the acceptable

quality limit (AQL) and limited quantity (LQ) limits for incoming sampling plans as well as the usual specification methods and acceptance criteria. Data collected in-coming and in-process can be used to determine compliance with a contract agreement. Per Q10, "Throughout the product lifecycle, companies are encouraged to evaluate opportunities for innovative approached to improve product quality" (1).

There are many ways, statistically, to achieve this goal. Trending, designed experiments, variability reduction, and design space are just some of the tools that can be used to make process improvements.

Many of the terms in ICH Q10 imply trending of critical parameters and attributes. It is a given that this must be done. Q10 states: "An effective monitoring system provides assurance of the continued capability of processes and controls to produce a product of desired quality and to identify areas for continual improvement" (1).

Process capability is measured by comparing the variability of the product/process to the width of the specification range. This comparison can best be achieved using statistical tolerance intervals because they take into account the sample size where Cpk and Ppk do not. Per Q10, "Identify sources of variation affecting process performance and product quality for potential continual improvement activity to reduce or control variation" (1).

Some Six Sigma programs have gotten a poor reputation in certain circles because of a single-minded focus on saving money as opposed to giving equal consideration to improving quality and reducing variation. It is the author's opinion that management needs to give equal attention and resources to both. As Q10 calls for, "Proposed changes should be evaluated by expert teams contributing the appropriate expertise and knowledge from relevant areas (e.g., Pharmaceutical Development, Manufacturing, Quality, Regulatory Affairs and Medical), to ensure the change is technically justified" (1). The company's statistics department or a statistician should be included in the team.

Many statements in ICH Q10 have important implications for the correct and consistent use of statistics in the day-to-day implementation of pharmaceutical quality systems. Addressing these harmonized recommendations proactively and in context can help to strengthen one's quality system and thereby reduce rejects and recalls.

References and notes

1. ICH, Q10 *Pharmaceutical Quality System* (2008).
2. ICH, Q8 *Pharmaceutical Development* (2009).
3. ICH, Q9 *Quality Risk Management* (2005).
4. L. Torbeck, *Pharm. Technol.* **35** (10) 46–47 (2011).
5. Note: Other definitions of Engineering Control exist in other industries.
6. Note: It is common practice to use only one to three of the eight Western Electric rules for a given control chart. It is counterproductive to use more than three rules at a time. **PT**

Measuring Growth in Big Pharma's Manufacturing Investment

Patricia Van Arnum

Pharmaceutical Technology's annual manufacturing investment update shows slight gains in biopharmaceutical manufacturing and emerging markets and continued restructuring of supply networks.

Measured growth. That is the best way to sum up the manufacturing investment activity of the pharmaceutical majors during the past year. Companies continue to implement restructuring programs as a way to reduce costs and optimize their manufacturing and supply networks. Investment, when it is made, is primarily in biologic-based manufacturing and emerging markets, with a few select projects proceeding in established product and geographic markets.

Company investment

Pfizer: Pfizer continues with plans to restructure its manufacturing network following its $68-billion acquisition of Wyeth in 2009. Following the acquisition, Pfizer's manufacturing sites totaled 81, and other acquisitions added 20 manufacturing sites. Pfizer subsequently exited nine sites and operated 90 plants as of the end of 2011, with major manufacturing facilities in Belgium, China, Germany, Ireland, Italy, Japan, Philippines, Puerto Rico, Singapore, and the United States. It plans to exit a further 10 sites during the next several years.

After the acquisition of Wyeth in 2009, Pfizer operated 20 R&D sites and has restructured its R&D operations, which involved several site closures, including its R&D facility in Sandwich, United Kingdom, except for a small presence there. In 2011, Pfizer rationalized several other R&D sites. It disposed of its toxicology site in Catania, Italy; exited its R&D sites in Aberdeen and Gosport, UK; and disposed of a vacant site in St. Louis, Missouri. Pfizer also shifted its cardiovascular, metabolic and endocrine disease and neuroscience research units from its site in Groton, Connecticut, to Cambridge, Massachusetts, where it signed a lease with the Massachusetts Institute of Technology, with occupancy anticipated in early 2014. In 2011, Pfizer opened Centers for Therapeutic Innovation laboratories in Boston, New York, and South San Francisco.

Novartis. In 2010, Novartis initiated a company-wide program to review its manufacturing footprint, which progressed in 2011, with major goals to create manufacturing centers of excellence, reduce its cost structure, and enhance utilization rates at strategic sites to 80% of capacity. To these ends, the company has announced the exit or partial exit of 14 sites since the program started in 2010. In Liverpool, UK, and Marburg, Germany, Novartis discontinued certain manufacturing activities to consolidate its influenza-vaccine platforms. Novartis also divested the pharmaceuticals division's sites in Casablanca, Morocco, and Huningue, France, and Sandoz (the generic-drug business of Novartis) sites in Jena, Germany, and Buenos Aires, Argentina. The company also discontinued pharmaceuticals manufacturing at sites in Tlalpan, Mexico, and Horsham, UK, and exited CIBA Vision production sites in Cidra, Puerto Rico, and Farnham, UK. Additionally, the company announced the discontinuation of certain manufacturing activities at its CIBA Vision site in Atlanta, Georgia, and the consolidation of pharmaceutical chemical operations in Switzerland, as well as closure of its chemical operations in Torre, Italy.

Novartis continues to make progress in the long-term redevelopment of its St. Johann headquarters site in Basel, Switzerland. This project, called "Campus," started in 2001 with the aim of transforming the site from one of primarily pharmaceutical production into a center of knowledge with a primary emphasis on international corporate functions and research activities. Through Dec. 31, 2011, the total amount paid and committed to be paid on the Campus Project was $2.1 billion. The company expects that through 2015, it will spend more than $2.5 billion and transfer production facilities to other sites in the Basel region.

Novartis continues to expand in emerging markets. In June 2011, Novartis began

Table I: Top 50 pharmaceutical companies (Rankings 1–25).

Rank	Company	2011 global pharmaceutical sales*	2011 R&D spending
1	Pfizer	$57.7 B	$9.112 B
2	Novartis	$54.0 B	$9.100 B
3	Merck & Co.	$41.3 B	$8.467 B
4	Sanofi	$37.0 B	$6.007 B
5	Roche	$34.9 B	$7.862 B
6	GlaxoSmithKline	$34.4 B	$5.822 B
7	AstraZeneca	$33.6 B	$5.033 B
8	Johnson & Johnson	$24.4 B	$5.138 B
9	Abbott	$22.4 B	$4.129 B
10	Eli Lilly	$21.9 B	$5.020 B
11	Bristol-Myers Squibb	$21.2 B	$3.800 B
12	Teva	$16.7 B	$1.080 B
13	Amgen	$15.3 B	$3.167 B
14	Takeda	$15.2 B	$3.466 B
15	Boehringer Ingelheim	$13.8 B	N/A
16	Bayer	$12.8 B	$1.979 B
17	Daiichi Sanyko	$11.6 B	$2.332 B
18	Novo Nordisk	$11.5 B	$1.662 B
19	Astellas	$11.4 B	$2.607 B
20	Gilead Sciences	$8.1 B	$1.229 B
21	Otsuka	$7.4 B	$1.974 B
22	Merck KGaA	$7.2 B	$1.577 B
23	Baxter International	$6.1 B	$946 M
24	Mylan	$5.5 B	$294 M
25	Servier	$5.0 B	$1.255 B

*Sales figures are global human prescription drug sales, inclusive of generic drugs and vaccines as far as company documentation provides. In most cases, numbers are taken from annual or SEC filings for the fiscal year ended in 2011, generally Dec. 31, 2011, for US and European companies and Mar. 31, 2011, for Japanese companies. In certain instances, estimates are used. For companies reporting in curencies other than US dollars, numbers are based on the average midpoint interbank rate for the month following the end of the fiscal year. Note: B is billion. M is million. R&D is research and development. N/A is not available. *Source*: The Pharm Exec 50, *Pharmaceutical Executive,* May 2012.

construction on a new $140-million manufacturing plant for pharmaceuticals and generic drugs in St. Petersburg, Russia. The plant is expected to produce approximately 1.5 billion units per year (oral solid dosage forms). In China, in 2007, Novartis opened a start-up facility for a new R&D center in Shanghai, China, and broke ground in 2008 on Phase 1 of a new facility that was originally to be home to approximately 400 R&D scientists and approximately 400 other pharmaceuticals division personnel. In 2009, it expanded the scope of the site with plans to invest $1 billion during the next five years to increase the size of its operations in Shanghai. Based on a re-evaluation of the site conducted in 2010, the current Phase 1 has been extended by two buildings. The cross-divisional Shanghai campus will house 800 offices and 400 laboratory workplaces.

In October 2010, Novartis announced plans to invest $600 million during the next five years to build new laboratory and office space for research activities in Cambridge, Massachusetts. In 2011, the company finalized design plans for the new buildings, received necessary zoning changes from the city of Cambridge, and began preparing the site for construction. In late 2010, Novartis began a construction project on the campus of Novartis in East Hanover, New Jersey, which will continue through 2013. The company expects that through 2013, it will spend more than $545 million to complete the construction and consolidate operations there.

In other recent investments, in June 2008, Novartis broke ground on a new $330-million rabies and tick-borne encephalitis manufacturing facility in Marburg, Germany. Construction is complete, and the facility is in the process of executing the necessary validation activities. Regulatory approvals for products are planned for 2012 and 2013. In November 2009, Novartis opened a new cell culture-based influenza vaccine manufacturing site in Holly Springs, North Carolina. As of December 31, 2011, the total amount spent on the project was $463 million, net of grants reimbursed by the US government. The total investment in this new facility is expected to be at least $900 million, partly supported by grants from the US government and prior investments in influenza cell- culture technologies at the Novartis vaccines site in Marburg, Germany. Novartis also began a project for a new $305-million vaccine-manufacturing facility in Recife, Brazil, with technical start-up of the facility planned for 2015. In 2011, Novartis' eye-care business, Alcon, completed the construction of a new $134-million manufacturing and R&D plant in Singapore; the plant is scheduled to produce saleable product after regulatory approval in 2012.

Novartis said it is making progress for resolving quality-control issues at its consumer healthcare operations in Lincoln, Nebraska, and at three facilities of Sandoz. In December 2011, Novartis suspended production at is Lincoln manufacturing site in conjunction with a voluntary recall of all lots of select, bottle-packaged configurations of certain over-the-counter products. In December 2011, FDA cited quality-control issues at three Sandoz manufacturing facilities in Broomfield, Colorado; Wilson, North Carolina; and Boucherville, Canada. In an Apr. 24, 2012, first-quarter earnings release, Novartis said that it is making progress in remediating the quality issues at the Lincoln site and the three Sandoz production sites.

Merck. Merck & Co. continues to move forward with restructuring. In Febru-

Table II: Top 50 pharmaceutical companies (Rankings 26–50).

Rank	Company	2011 global pharmaceutical sales*	2011 R&D spending
26	Mitsubishi Tanabe	$4.7 B	$788 M
27	Celgene	$4.7 B	$1.600 B
28	CSL	$4.5 B	$349 M
29	Allergan	$4.4 B	$902 M
30	Forest Laboratories	$4.2 B	$715 M
31	Dainippon Sumitomo	$4.0 B	$817 M
32	Shire	$4.0 B	$770 M
33	Menarini	$3.9 B	N/A
34	Biogen Idec	$3.8 B	$1.219 B
35	Eisai	$3.7 B	$1.740 B
36	UCB	$3.7 B	$1.004 B
37	Watson Pharmaceuticals	$3.7 B	$295 M
38	Purdue	$2.9 B	N/A
39	Lundbeck	$2.7 B	$620 M
40	Warner Chilcott	$2.7 B	$107 M
41	Kyowa Hakko Kirin	$2.7 B	$543 M
42	Shionogi	$2.6 B	$611 M
43	Hospira	$2.6 B	$358 M
44	Valeant Pharmaceuticals	$2.4 B	$65 M
45	Endo Pharmaceuticals	$2.2 B	$182 M
46	Actavis	$2.0 B	N/A
47	Griflos	$1.9 B	$98 M
48	Actelion	$1.8 B	$486 M
49	Galderma	$1.8 B	$363 M
50	Aspen	$1.7 B	$1.3 M

Sales figures are global human prescription drug sales, inclusive of generic drugs and vaccines as far as company documentation provides. In most cases, numbers are taken from annual or SEC filings for the fiscal year ended in 2011, generally Dec. 31, 2011, for US and European companies and Mar. 31, 2011, for Japanese companies. In certain instances, estimates are used. For companies reporting in curencies other than US dollars, numbers are based on the average midpoint interbank rate for the month following the end of the fiscal year. Note: B is billion. M is million. R&D is research and development. N/A is not available. *Source*: The Pharm Exec 50, *Pharmaceutical Executive,* May 2012.

ary 2010, subsequent to the Merck and Schering-Plough merger, Merck began a global restructuring program in conjunction with the integration of the two companies. In July 2011, the Merck announced the latest phase of the restructuring program, which included a further reduction of its workforce of 12–13% company worldwide. A majority of the workforce reductions in this phase relate to manufacturing (including animal health), administrative, and headquarters organizations. Previously announced workforce reductions of of 17% in the earlier phases of the program primarily reflected the elimination of positions in sales, administrative and headquarters organizations, as well as from the sale or closure of certain manufacturing and R&D sites and the consolidation of office facilities.

Sanofi. Sanofi's subsidiary Genzyme began production of the enzyme-replacement therapy Fabrazyme (agalsidase beta) at its new facility in Framingham, Massachusetts, following approval of the facility by FDA and EMA in January 2012. In May 2012, EMA and FDA approved a second operation for fill–finish at Genyzme's Waterford, Ireland, manufacturing plant, which nearly doubled capacity for fill–finish for Myozyme and Lumizyme (alglucosidase alfa) at the 4000-L scale. These developments follow a 2010 consent decree issued by FDA to Genzyme for manufacturing violations at its Allston, Massachusetts, facility and resulting requirements to transfer fill–finish production out of that facility. Other investments by Genzyme include expansion of Myozyme production capacity in Geel, Belgium, Fabrazyme in Framingham, Massachusetts, Thymoglobulin (anti-thymocyte globulin (rabbit)) in Lyon, France, and the filling operations in Waterford, Ireland.

Other recent investments by Sanofi are in two new Lantus production lines in Frankfurt, which complemented an earlier acquisition of the Diabel manufacturing site from Pfizer, to expand insulin production. Sanofi invested in its Brindisi, Italy, site to expand production of spiramycin, the API in the antibiotic Rovamcyin. The company also is investing in the launch of epiCard, a gas-powdered single-dose, single-use, auto-injector for epinephrine.

Sanofi is continuing with its Biolaunch project, which is designed to converts its chemical facilities to biotechnology-based production. It is on track to create a monoclonal antibody production facility at its site in Vitry-sur-Seine, France, and is investing in new biosynthetic processes as its sites in Saint-Aubin-Les Elbeuf and Vertaolaye, France. In May 2009, Sanofi began construction of a new EUR 300 million ($364 million) manufacturing center in Neuville-dur Saône, with the the goal to progressively transition existing chemical production to vaccine production beginning in 2013. Sanofi Pasteur, the vaccine arm of Sanofi, is scheduled to begin commercial production of a new antigen production unit in Mexico for seasonal and pandemic influenza vaccines in 2012, once the necessary production and marketing approvals have been obtained from Mexican regulatory authorities.

In emerging markets, in May 2012, Sanofi inaugurated a new assembling and packaging line for producing its prefilled insulin injection pen Lantus SoloStar at its facility in Beijing. The company announced a second phase $90-million project to install a cartridge aseptic product line at the facility. The facility has a designed capacity of 48 million units. Sanofi is building a new manufacturing site in Hangzhou,

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China, to replace an existing manufacturing site there, which is scheduled to be completed in 2012. The company reached an agreement with the King Abdulah Economic City to build a manufacturing facility for solid-dosage forms in Saudi Arabia.

Roche. In 2011, Roche executed 25 major engineering projects. Key projects included transforming its manufacturing facility for solid dosage forms in Shanghai from a local to a global supply operation. In early 2011, the facility received FDA and EMA approvals to produce Xeloda (capecitabine) for the US and EU markets.

In June 2011, Roche completed a CHF 191-million ($193 million) expansion at it facility in Penzberg, Germany, which upgraded and expanded the site's therapeutic protein development and production capacity. In November 2011, Roche completed construction of a new CHF 250 million ($252 million) technical R&D facility in Basel, Swizterland. The facility houses laboratories, offices, and small-scale production lines. In late 2010, Roche divested technical development and small-molecule manufacturing operations in Boulder, Colorado, to Corden Pharma. Corden will continue to supply Roche with commercial-scale peptides and chemical APIs. Roche also sold its clinical plant in Oceanside, California to Gilead Sciences.

GlaxoSmithKline. In March 2012, SmithKline (GSK) announced plans to invest more than £500 million ($798 million) in the UK across its manufacturing sites, which included selecting Ulverston in Cumbria as the location for the first new GSK manufacturing facility to be built in the UK in almost 40 years. The company also will invest in sites in Montrose and Irvine, Scotland.

GSK's announcement followed plans by the UK government to implement a "patent box" to encourage investment in R&D and related manufacturing in the UK by introducing a lower rate of corporation tax on profits generated from UK-owned intellectual property. Following a feasibility study conducted through 2011, GSK said it will locate a new £350 million ($559 million) biopharmaceutical manufacturing facility in Ulverston, Cumbria. Detailed planning and design of the new facility is underway with an anticipated start date for construction of 2014–2015, dependent on portfolio timing and obtaining necessary planning and related consents. Once construction starts, it is likely to take at least six years before the plant is fully operational.

"The introduction of the patent box has transformed the way in which we view the UK as a location for new investments, ensuring that the medicines of the future will not only be discovered, but can also continue to be made here in Britain".
—GSK's CEO Andrew Witty, Mar. 22, 2012.

GSK also reported in March 2012 that it is considering additional manufacturing investment at Ulverston, which could double the total investment at the site to approximately £700 million ($1.1 billion). GSK will invest more than £100 million ($160 million) in its two manufacturing sites in Scotland: an expansion at Montrose for key materials for its respiratory drug and aluminum adjuvants for vaccines and expanded antibiotic production capacity at Irvine. GSK will also invest in sustainable green-energy production and environmentally friendly manufacturing technologies at both sites. The company is making other investments totaling £80 million ($128 million) at its sites in Ware in Hertfordshire to increase manufacturing capacity for its respiratory-inhalation device and at Barnard Castle in County Durham to establish a dermatology-manufacturing center of excellence.

As GSK proceeds with new manufacturing investment, it continues to restructure. In 2011, GSK met its original target of £2.2 billion ($3.4 billion) in annual cost-savings and identified additional annual savings of approximately £600 million ($931 million), bringing expected total annual savings of £2.8 billion ($4.3 billion) by 2014. GSK has cut its pharmaceutical R&D footprint by more than 45% during the past three years from 494,000 m^2 to 295,000 m^2. During the same period, its manufacturing organization has achieved annual savings of approximately £600 million ($931 million) . Since 2006, GSK has exited 19 manufacturing sites, including selling or closing four factories in 2011, thereby reducing its total number of manufacturing sites to 74.

AstraZeneca. In February 2012, AstraZeneca announced new restructuring initiatives aimed at delivering annual cost-savings of $1.6 billion by the end of 2014. The restructuring will reduce headcount by 7300. The job cuts include 1350 positions in supply-chain and manufacturing operations and 2220 positions in R&D, including ending R&D activity at sites in Sodertalje, Sweden, and Montreal.

Overall, AstraZeneca's capital expenditures on supply and manufacturing facilities were approximately $388 million in 2011 (2010: $333 million; 2009: $360 million). At the end of 2011, approximately 9600 people at 23 sites in 16 countries were working on the manufacturing and supply of products. In October 2011, AstraZeneca announced an investment of $200 million to build a manufacturing facility in China Medical City in Taizhou, Jiangsu province, China, to meet growing local demand.

Bristol-Myers Squibb. In May 2012, FDA approved Bristol-Myers Squibb's biologics manufacturing facility in Devens, Massachusetts, for commercial production of the company's arthritis drug Orencia (abatacept). The $750-million multiproduct bulk biologics manufacturing facility in Devens represented the largest capital project in the company's history. **PT**

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Bioavailability Enhancement: When to Use Hot-Melt Extrusion versus Spray Drying

A Q&A with Bend Research

Enhancing bioavailability can be achieved through hot-melt extrusion (HME) or spray drying. The drug product's API properties and stage of development are important factors to consider when deciding which technique to use. There are also considerations to be made with regard to process, time, and cost. To gain perspective on these issues as well as insight into more recent advances in HME and spray drying, *Pharmaceutical Technology* spoke to Bend Research, an independent drug-formulation development and manufacturing company based in Bend, Oregon.

Choosing the right technique

PharmTech: One tool for bioavailability enhancement is to create amorphous solid dispersions through such processes as hot-melt extrusion (HME) or spray drying. What factors come into play when deciding whether to produce the amorphous solid dispersions through HME or spray drying?

Bend Research: Both spray drying and HME can be used to produce amorphous dispersions that enhance the bioavailability of poorly soluble compounds. There are a number of factors that come into play when deciding to progress an amorphous dispersion. These include performance, projected dose, stability, and manufacturability. When choosing which technology to employ for optimizing the amorphous dispersion formulation's performance, two key factors are: the physical-chemical properties of the API and the phase of development, which influences the amount of API available for formulation development.

Important physical–chemical properties include the solubility of the API in either a solvent (for spray drying) or polymer (for HME), the melting temperature of the API, and the LogP value of the API. For spray drying, the solubility of the API in the solvent is crucial to ensure a readily scalable and viable process, whereas for HME, the solubility of the API in the polymer is crucial to ensure a thermodynamically stable system. The particle size of the API, which influences the dissolution rate during processing, can also be crucial for complete dissolution into the polymer melt.

The processing temperature is important for HME because the API must either melt to form a dispersion or dissolve through high shear forces into the molten polymer. If the processing temperature is too high, the compound or the polymer used in the formulation can degrade. Typically, 200 °C to 225 °C is regarded as the upper processing-temperature limit for an effective HME process. Although compounds can be extruded at higher processing temperatures, this physical situation often produces a partially crystalline formulation instead of an amorphous dispersion.

The phase of development is also an important factor in process selection. For example, for early-stage or discovery-support activities, API availability is often limited. This limited API availability tends to make spray drying the preferable process because its feasibility can be determined with as little as 50 to 100 mg of API, whereas several grams of API are typically required to develop an initial HME process. For APIs that are amenable to HME, typically after proof-of-concept clinical studies, when hundreds of grams of API are available, an initial spray-drying process can be converted from spray drying to HME.

Advantages and disadvantages of each technique

PharmTech: What are the advantages and disadvantages of using HME compared with spray drying to produce the amorphous solid dispersion?

Bend Research: HME has two primary advantages. First, no solvents are used, so solvent cost and recovery are not a factor in cost-of-goods or environmental health and safety considerations. Second, the equipment footprint for HME is relatively small when the process is scaled up.

The primary disadvantage of HME is that the compound must be melted or dissolved in molten polymer at high temperatures. Thus, it is less applicable to compounds with higher melting temperatures or those that are thermally labile. This disadvantage can be partially remedied by including nonvolatile and volatile plasticizers in the formulation, which lower the temperatures required to produce an amorphous dispersion. Because an ideal amorphous dispersion is homogeneous at the molecular level, a second disadvantage is that the homogeneity of the final dispersion can be affected by process parameters such as temperature, screw configuration, screw speed, and feed rates; this aspect, combined with the relatively large minimum batch size, results in cost and risk during early development.

PharmTech: What are the advantages/disadvantages of using spray drying compared with HME to the amorphous solid dispersion?

Bend Research: Spray drying offers the following advantages: it is applicable to a broader chemical space for the API and types of dispersion polymers that can be used (due to dissolution of the API in a volatile organic solvent); it does not expose the API to excessive heat during manufacture of the amorphous dispersion; and it can be scaled down, requiring smaller quantities of API during formulation screening.

Spray drying has a few disadvantages as well: solvents are used and must be recovered, equipment footprints are larger, and capital and operating costs are higher. These considerations must be taken into account when designing later-stage or commercial processes and facilities, but they are not insurmountable—as evidenced by successful operation of Hovione's PSD-4 and PSD-5 spray-drying facilities and the fact that spray drying is used extensively outside of the pharmaceutical industry at large scales.

Achieving desired bioavailability

PharmTech: Can you be specific in terms of achieving desired bioavailability/solubility of the resulting product, stability of the resulting product, the ease and/or scalability of the manufacturing process, and other process conditions that are important in deciding which approach to use?

Bend Research: As mentioned previously, both spray drying and HME can be used effectively to manufacture amorphous dispersions. A formulation produced by either process would be expected to yield similar bioavailability and physical stability as long as both processes yield a homogeneous amorphous dispersion with appropriate final-powder particle size, which generally requires milling for HME. If either of the processes fails to produce a homogeneous amorphous dispersion, the resulting formulation will likely underperform. This situation is most common when a compound fails to completely dissolve during the HME process due to either the high melting temperature of the compound, or the low solubility of the compound in the molten polymer, resulting in crystallization or phase separation when the melt cools.

Spray drying and HME are readily scaled. Commercial-scale equipment is available at many pharmaceutical organizations and several contract research organizations.

Recent advances

PharmTech: On an industry level, can you highlight recent advances in HME with respect to improvements in the manufacturing process and its application to different types of APIs?

Bend Research: HME is a technology that has been widely used in pharmaceutical and nonpharmaceutical industries for decades. Recent advances in HME include efforts to reduce processing temperatures by including plasticizers and reduce the residence time of the compound and polymer during processing. Numerous research groups are looking at nonvolatile plasticizers, such as vitamin E or triethyl citrate, to reduce processing temperatures. Others have reported the use of volatile excipients, such as supercritical carbon dioxide, to avoid decreases in the final dispersion's glass-transition temperature that occur with traditional plasticizers.

There have also been recent reports of the use of equipment that has significantly reduced residence time. Professor McGinity's research group at the University of Texas has developed a process called Kinetisol to make amorphous dispersions. It is based on equipment that was developed to recycle plastics, which can reduce the residence time of the API and polymer at processing temperatures from minutes to tens of seconds.

PharmTech: Can you highlight recent industry advances in spray drying with respect to improvements in the manufacturing process and its application to different types of APIs?

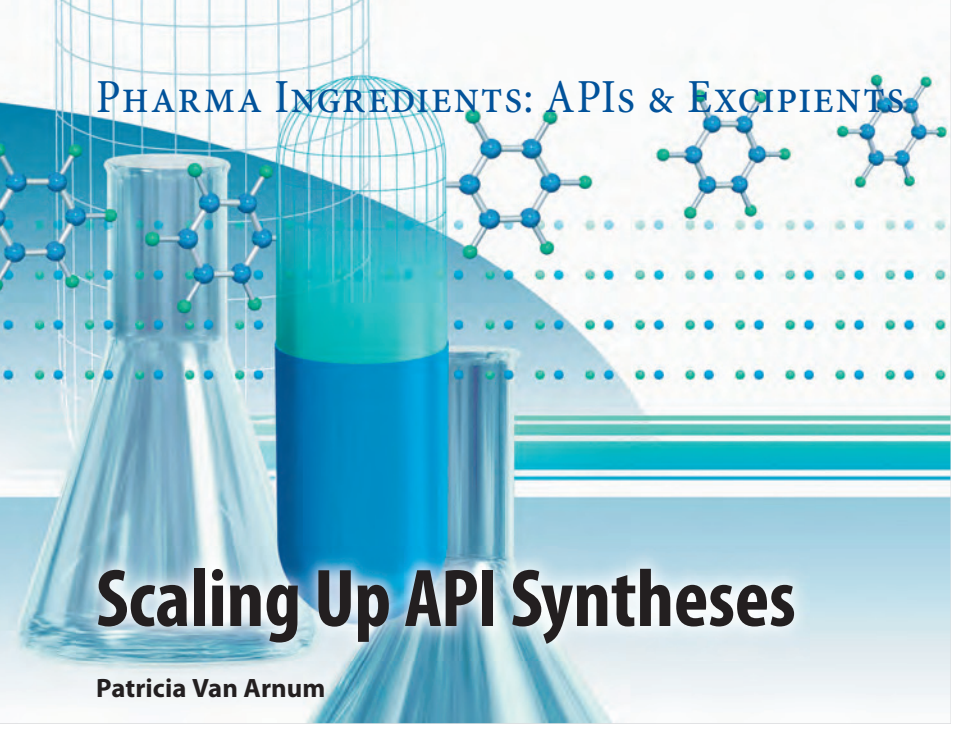
Bend Research: Although spray drying is a well-established process, innovations in formulation approaches and process equipment are occurring. In formulation, there is an increasing need for a third component in the dispersions to help deliver challenging compounds aimed at novel biological targets. Often, a surfactant is added to help increase the dissolution rate or dispersion-particle wetting or to provide an alternate micelle source to enhance drug solubility *in vivo*.

Equipment advances include novel spray-dryer and cyclone designs to collect the dispersion particles more efficiently. This is especially significant for particle-engineering applications such as inhalation, which requires the manufacture and collection of particles with a narrow particle-size distribution for delivery to the lung.

As part of the effort to formulate compounds with low solubility in organic solvents, Bend Research has developed a "hot process," which allows a drug suspension to be heated to high temperatures—often well above the ambient-pressure boiling point of the solvent—in a heat exchanger to dissolve the drug immediately before it is introduced into the spray dryer. This decreases solvent use and can result in a more scalable process.

PharmTech: One specific technology of Bend Research is the spray-dried nanoadsorbate technology. Can you explain this technology and how it differs from conventional spray drying?

Bend Research: Two physical situations are dose-limiting when formulating amorphous dispersions: low dissolution rates for compounds that are highly lipophilic and recrystallization for compounds that have high melting temperatures. To formulate highly lipophilic compounds, we have developed the spray-dried nanoadsorbate technology as an extension of spray-dried dispersions. This technology is based on spray drying an amorphous dispersion onto a high-surface-area inorganic support such as Cab-O-Sil (fumed silica). The increased surface area promotes faster dissolution of the dispersion and is particularly well suited for highly lipophilic compounds (e.g., compounds that have LogP values greater than 6 to 7). Similarly, to formulate compounds with high melting temperatures, we have developed a technology that is based on intentionally recrystallizing the compounds in the dispersion polymer in nanometer-sized domains. This formulation type also is a high-energy form of the API that contains a concentration-enhancing polymer. **PT**



Scaling Up API Syntheses

Patricia Van Arnum

Approaches center on ways to optimize process conditions and operability.

Process chemists face the challenge of developing cost-effective and efficient commercial manufacturing routes for APIs. They encounter the challenges of increasing product yield, achieving greater stereoselectivity and regioselectivity, and improving process conditions, such as temperature and pressure, all in a means to produce a high-quality pharmaceutical compound in a safe manner. A variety of tools may be used in this effort, including the application of green-chemistry approaches, such as biocatalysis, solvent replacement, and continuous-flow chemistry, to help achieve more efficient chemical transformations under improved reaction conditions.

Biocatalytic route to simvastatin

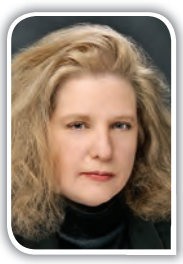
In June 2012, Codexis, a company specializing in biocatalysis, and Yi Tang, professor in the Department of Chemical and Biomolecular Engineering at the University of California at Los Angeles (UCLA), were awarded the "2012 Greener Synthetic Pathways Award" as part of the Environmental Protection Agency's (EPA) Presidential Green Chemistry Challenge Awards for developing a biocatalytic route for making simvastatin, the active ingredient in Merck & Co.'s anticholesterol drug Zocor, which is now off patent (1). Codexis and Tang won the award this year after having made prior submissions of the new process in 2010 and 2011 (2–4).

For the simvastatin route, Codexis licensed technology from Tang. The previous synthetic routes to simvastatin involved converting lovastatin into simvastatin by adding a methyl group that required protecting and then deprotecting other functionalities in the lovastatin molecule in a multistep synthesis. In the first route, lovastatin was hydrolyzed to the triol, monacolin J, followed by protection with selective silylation, esterification with dimethyl butyryl chloride, and deprotection. The second route involved protecting the carboxylic acid and alcohol functionalities, methylating the C2' carbon with methyl iodide, and deprotecting the product. These routes were inefficient because they produced less than 70% overall yield and were mass-intensive due to protection and deprotection (1–4).

The route developed by Tang and his group circumvented protection and deprotection and resulted in greater atom economy, reduced waste, and overall less hazardous reaction conditions. First, they cloned LovD, a natural acyltransferase produced by *Aspergillus terreus* that is involved in synthesizing lovastatin and that can accept nonnatural acyl donors. Recognizing that LovD might be a type of simvastatin synthase and a starting point for creating a new biocatalytic process, they evolved the enzyme toward commercial utility (1–5). Codexis licensed Tang's technology, engineered the enzyme further, and optimized the simvastatin manufacture.

The biocatalyst LovD selectively transferred the 2-methylbutyryl side chain to the C8 alcohol of monacolin J sodium or ammonium salt. The acyl donor, dimethylbutyryl-*S*-methylmercaptopropionate (DMB-SMMP), is efficient for the LovD-catalyzed reaction, is safer than traditional alternatives, and is prepared in a single step from inexpensive precursors, according to the awards summary report (1). Codexis licensed this process from UCLA and subsequently optimized the enzyme and the chemical process for commercial manufacture. Codexis carried out nine iterations of *in vitro* evolution, creating 216 libraries and screening 61,779 variants to develop a LovD variant with improved activity, in-process stability, and tolerance to product inhibition (1). The approximately 1000-fold improved enzyme and the new process pushed the reaction to completion at high substrate loading and minimized the amounts of acyl donor and of solvents for extraction and product separation. In the new route, lovastatin is hydrolyzed and converted to the water-soluble ammonium salt of monacolin J (1–5).

As specified in the Presidential Green Chemistry Challenge Awards summary report, the genetically evolved variant of LovD acyltransferase from *Escherichia coli* uses DMB-SMMP as the acyl donor to make the water-insoluble ammonium salt of simvastatin. The only coproduct of simvastatin synthesis is methyl 3-mercaptopropionic acid, which is recycled. The



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final yield of simvastatin ammonium salt is more than 97% at a loading of 75 g/L of monacolin J. It avoids the use of several hazardous chemicals, including *tert*-butyl dimethyl silane chloride, methyl iodide, and *n*-butyl lithium. More than 10 metric tons of simvastatin have been manufactured using this new process (1).

Biocatalytic route to atorvastatin

Pfizer also employed a more environmentally approach in developing a biocatalytic route to making atorvastatin, the active ingredient of Lipitor and submitted the process as an entry for consideration to the EPA's Presidential Green Chemistry Challenge Awards (1). The new process incorporated a water-based 2-deoxyribose-5-phosphate aldolase (DERA) enzyme at the beginning of the route to make a lactol from an amino aldehyde (i.e., 3-phthalimidopropionaldehyde; PPA) and acetaldehyde (1).

The synthesis eliminated the use of cyanide or azide moieties to introduce nitrogen because it is already present in the lactol. In contrast to the original synthesis, the DERA enzyme set both stereocenters with high selectivity in water at room temperature. Converting the resulting lactol into isopropyl acetonide atorvastatin (IAA) involved only four high-yield chemical steps (oxidation, esterification, deprotection, Paal Knorr). The IAA product was isolated as a solid, and IAA was converted to atorvastatin (1). The new synthesis eliminated the previous high-pressure hydrogenation step with its associated metal catalysts. It also avoided pyrophoric *n*-butyl lithium and its associated butane waste gas. FDA approved the new manufacturing process in April 2010, and Pfizer manufactured commercial-scale validation batches in 2011 and is currently transitioning to full-scale commercial manufacture, according to the EPA's Presidential Green Chemistry Challenge Awards report (1).

Eli Lilly's Grignard chemistry

The Grignard reaction is a well-established reaction in organic chemistry but it poses some challenges in scaling up to commercial scale: strongly exothermic activation and reaction steps; heterogeneous reactions with potential problems suspending

Computational modeling: drug interactions

An ongoing challenge for scientists involved in drug development is to develop methods that allow them to identify drugs of clinical efficacy with minimal side effects. A team of researchers at the Novartis Institutes for Biomedical Research, the University of California San Francisco (UCSF), and Sea Change Pharmaceuticals, a start-up company from UCSF and the QB3 California Institute for Quantitative Biosciences, recently developed a new set of computer models to help researchers identify drug candidates that are most likely to have adverse side effects. The models enable a computational approach to drug-safety assessments.

Specifically, the researchers used a computational approach to predict the activity of 656 marketed drugs on 73 unintended so-called side-effect targets (1). They evaluated which of the 656 drugs were most likely to bind to 73 target proteins that appear on Novartis' safety panel for testing drugs for side effects, according to June 11, 2012, UCSF press materials (2). The computer model identified 1241 possible side-effect targets for the 656 drugs, of which 348 were confirmed by the Novartis proprietary database of drug interactions and another 151 were hits for other side effects that had not been previously identified for these drugs but which were later confirmed with additional laboratory testing (2).

Overall, approximately half of the predictions were confirmed, either from proprietary databases unknown to the method or by new experimental assays. The researchers developed an association metric to prioritize new off-targets that explained side effects better than any known target of a given drug, thereby creating a drug–target–adverse drug reaction network (1). This computational approach for identifying drug interactions is important to identify drugs of greater risk and eliminate them in the drug-development process and also provides the potential of developing new indications or uses of existing drugs (2).

Sources

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and mixing the reaction mixture; and operational hazards posed by ethereal solvents such as diethyl ether (1). Eli Lilly developed safer Grignard chemistry using a continuous stirred tank reactor (CSTR) that allows continuous formation of Grignard reagents with continuous coupling and quenching operations, a process in which the company submitted an entry to the 2012 EPA Presidential Green Chemistry Challenge Awards (1). According to the entry, the CSTR approach mitigated hazards by operating at a small reaction volumes, performed metal activation only once for each campaign, and used 2-methyltetrahydrofuran as a Grignard reagent and reaction solvent, resulting in products with enhanced chemo- and stereoselectivity. Relative to batch processing, the continuous approach allowed steady-state control and overall reductions up to 43% in magnesium, 10% in Grignard reagent stoichiometry, and 30% in process mass intensity (1).

Biocatalysis can produce more efficient chemical transformations.

Improved solvents for making diaryl aldimines

Imines are intermediates used in many pharmaceutical syntheses. Diaryl aldimines, for example, are used in the synthesis of the anticancer drug Taxol (paclitaxel) and the anticholesterol drug Zetia (ezetimibe) (1). Traditional syntheses of diaryl aldimines often require hazardous solvents and include energy-intensive, multihour reflux steps. Although some imine syntheses use more benign solvents or conditions, they still require long reaction times, recrystallization, or other environmentally harsher procedures. Jacqueline Bennett, professor in the Department of Chemistry and Biochemistry, State University of New York (SUNY) Oneonta and the SUNY Research Foundation, developed a process that used ethyl L-lactate as a solvent to synthesize imines. The process was submitted as an entry to the 2012 US EPA's Presidential Green Chemistry Challenge Awards (1). According to the awards summary report, the method was efficient under ambient conditions, required less solvent than other methods, had a median yield of more than 92%, and had a median reaction time of less than 10 min (1). The resulting imines were generally sufficiently pure without recrystallization as the polarity of ethyl L-lactate was modulated by adding water. The starting materials remained dissolved, but the imine crystallized out of solution as it formed (1). Although traditional methods often drive reactions forward by removing water, this method drove the reaction forward by removing the product through crystallization, according to the summary report (1). Bennett and her research team have synthesized nearly 200 imines using this method and filed a US patent for the process (1, 6).

Ethylene in fine-chemical synthesis

Another interesting entry to the US EPA's Presidential Green Chemistry Challenge Awards involved the use of ethylene in fine-chemical synthesis developed by T. V. RajanBabu, professor in the Department of Chemistry, Ohio State University (1). According to the awards summary report, practical methods using carbon feedstock sources as starting materials to form enantioselective carbon–carbon bonds are not common. A broadly applicable reaction using ethylene to install vinyl groups enantiomerically, as developed by RajanBabu, could have significant impact in fine-chemical synthesis.

RajanBabu and his team developed highly catalytic (substrate–catalyst ratio up to 7,412:1) protocols for nearly quantitative (isolated yields of more than 99% and highly selective (approximately 100% regioselectivity; enantiomeric ratios of more than 99:1) codimerization of ethylene and various functionalized vinylarenes, 1,3-dienes, and strained alkenes. These

reactions proceeded under mild conditions (–52 °C to 25 °C; 1 atmosphere of ethylene) to produce intermediates, such as 3-arylbutenes, which can be transformed to nonsteroidal anti-inflammatory drugs (NSAIDs) in two steps. These reactions consume both starting materials, leaving no side products. Successes include highly enantioselective syntheses of common NSAIDs, such as ibuprofen, naproxen, flurbiprofen, and fenoprofen, from the corresponding styrenes and ethylene (1).

Cyclic and acyclic 1,3-dienes also underwent efficient enantioselective addition of ethylene. Syntheses of several 1-vinylcycloalkenes and 1-substituted-1,3-butadienes achieved yields up to 99% (1). The approach has also been applied to other biologically relevant classes of compounds, including bisabolanes, herbindoles, trikentrins, steroid D-ring 20S- or 20R-derivatives, (–)-desoxyeseroline, pseudopterosin A–F, G–J, and K–L aglycones, and helioporins (1).

Impurity scavengers

Chemicals, intermediates, and reagents as well as byproducts of synthetic processes can have toxic properties and be present as impurities at low levels in an API or final drug formulation. The detection and removal of these impurities are of crucial importance to process chemists, particularly in the case of genotoxic impurities. One of the potentially genotoxic impurities based on structural alerts is acrolein, an α, β-unsaturated aldehyde that is used as a building block in the production of pharmaceuticals (7).

Researchers at MIP Technologies, a subsidiary of Biotage, and the Universität Dortmund in Germany recently reported on an approach for selective removal of acrolein from APIs using iodixanol as a model API. The acrolein scavenging performance of polystyrene- and silica- based aldehyde scavengers in organic media in the presence of the API iodixanol was tested. Several scavengers were tested, and the resins that the showed highest binding efficiency and selectivity were further evaluated. The most effective and selective scavenging was obtained with polystryene–amine, which removed up to 97.8% of acrolein and only 2.0% of iodixanol within 20 min using a batch-mode extraction procedure (7).

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Improving protein purification through high-performance membranes

As pharmaceutical companies intensify their product-development efforts in biologic-based drugs, strategies to improve upstream and downstream processing are crucial. Researchers at Michigan State University (MSU) recently developed new high-performance membranes to facilitate protein purification. The researchers were trying to resolve some of the challenges in column-based affinity separations by using porous membranes but waned to mitigate the problem of low binding capacities comparative to traditional columns (1).

"The membrane devices that we've manufactured can simplify protein purification by rapidly capturing the desired protein as it flows through membrane pores," said Merlin Bruening, in an Apr. 30, 2012, MSU press release, who has patented the process and is working to scale up his invention. "Our membranes have two to three times more capacity than existing commercial devices, and they should reduce the purification process time substantially. Typically, our procedures are complete in 30 minutes or less."

Bruening and his team were trying to grow extended polymer chains in the membranes in a multistep, oxygen-free process. In doing so, they found that direct adsorption of acidic polymers at low pH was much simpler yet accomplished the same task of creating extended polymer in the pores, according to the MSU release, as the purification used adsorption to attract contaminants to the surface rather than absorption. "Once our findings began steering us toward the simpler solution, we began developing simple processes to modify membranes by simply flowing polymer solutions through the membranes," Bruening said in the MSU press release.

Specifically, the researchers found that layer-by-layer polyelectrolyte adsorption was a simple, convenient method for introducing ion-exchange sites in porous membranes. The researchers showed that adsorption of poly(acrylic acid) (PAA)-containing films at pH of 3 rather than pH of 5 increased the protein-binding capacity of such polyelectrolyte-modified membranes three- to six-fold (1). The low adsorption pH generated a high density of –COOH groups that functioned as either ion-exchange sites or points for covalent immobilization of metal-ion complexes that selectively bind tagged proteins. Derivatization of the free –COOH groups by reaction with aminobutyl nitrilotriacetate (NTA) yielded metal ion complexes that selectively bound tagged proteins. Although modification with polyelectrolyte films occurred by simply passing polyelectrolyte solutions through the membrane for as low as 5 min, with low-pH deposition, the protein-binding capacities of such membranes were as high as for membranes modified with polymer brushes and two to three-fold higher than for commercially available immobilized metal affinity chromatography resins (1). The researchers concluded that polyelectrolyte adsorption at low pH is much simpler than growth of polymer brushes in membranes, and the binding capacities that result from the two modification methods are similar. They reported that derivatization of PAA/polyethyleniminePAA-modified membranes with NTA-Ni^{2+} complexes yields materials that selectively capture His-tagged protein with > 90% recovery (1).

Source

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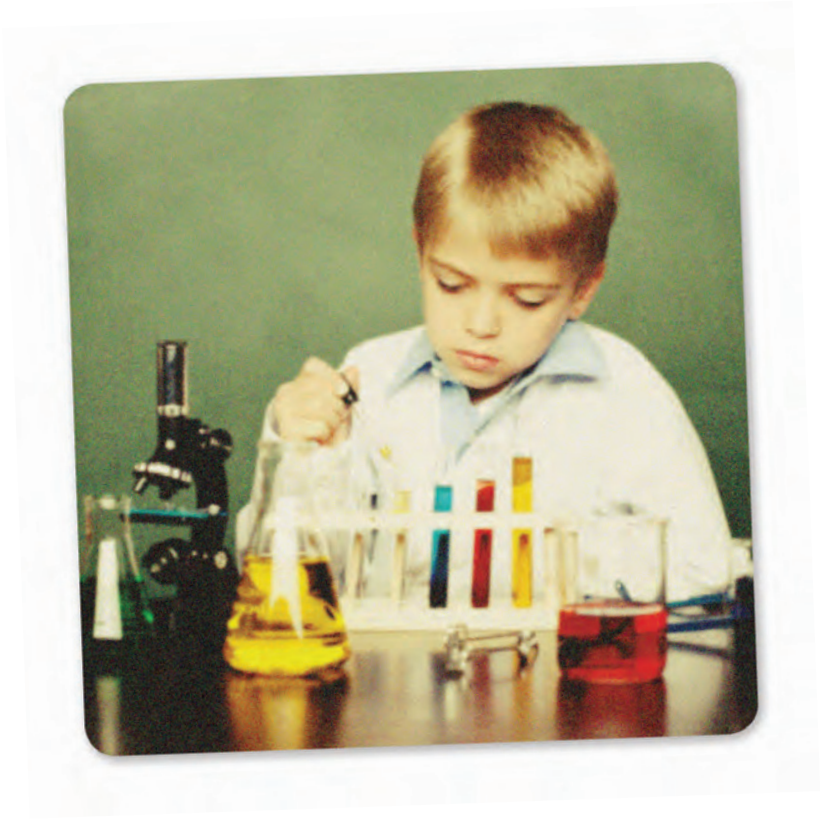
Remember your first chemistry set?



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Carbon Measurement Methods for Cleaning Validation

Comparing Direct Combustion with Rinse and Swab Sampling Methods.

Robert Clifford and Minako Tanka

TOC-LCPH, SHIMADZU

Cleaning validation provides assurance that the quantity of residual substances collected from equipment surfaces are within permissible limits, helping to ensure quality control and safety in pharmaceutical manufacturing facilities. Three different cleaning validation methods for measuring the carbon in residual samples of various pharmaceutical substances were compared.

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The challenges of conducting cleaning validation are documented in the literature. R. Baffi et al., for example, described the diverse analytical challenges arising in validating cleaning procedures for biopharmaceutical products produced by recombinant DNA, in which a broad range of potential residual cellular components and trace levels of detergents must be quantified (1). M.A. Strege et al. described the total organic carbon (TOC) analysis of swab samples for cleaning validation of bioprocess fermentation equipment and discussed accuracy, limits of detection, limit of quantitation, linearity, and precision (2). K.M. Jenkins et al. compared the advantages and disadvantages of multiple methods for cleaning validation, including high-performance liquid chromatography (HPLC), thin-layer chromatography (TLC), spectrometry, TOC, and conductivity (3). A.J. Holmes et al. described the TOC method for measuring residual aspirin on aluminum, stainless steel, painted carbon steel, and Plexiglas (4). The latter two authors describe the swab challenge as noted in the FDA guide to inspections of cleaning surfaces.

For cleaning validation using a TOC analyzer, the following types of sampling methods are available:

- rinse sampling
- swab sampling with aqueous extraction
- swab sampling with direct combustion.

These methods were compared using a total organic carbon analyzer (TOC-LCPH, Shimadzu) to measure residual pharmaceutical products and their constituent substances.

Preparation of residue samples

Residue samples were prepared by applying various types of pharmaceutical products and their constituents to stainless steel pots. Compounds with varying levels of water solubility (i.e., soluble, insoluble, and very insoluble) were evaluated to determine how each method performed. The water-soluble substances were dissolved in water and the water-insoluble substances were dissolved in ethanol or acetone, as shown in **Table I**. Solution concentrations were adjusted to 2,000 mgC/L (i.e., carbon concentration of 2000 mg/L).

The carbon contents of tranexamic acid ($C_8H_{15}NO_2$), anhydrous caffeine ($C_8H_{10}N_4O_2$), isopropylantipyrine ($C_{14}H_{18}N_2O$), and nifedipine ($C_{17}H_{18}N_2O_6$) were estimated by molecular formula. Carbon contents of Gentashin ointment (aminoglycoside antibiotic) and Rinderon ointment (corticosteroid) were determined with the TOC analyzer by adding samples of the ointments directly into a solid-sample combustion unit (SSM-5000A, Shimadzu) since molecular formula for these compounds are unknown.

Each residue sample consisted of a 5-cm^2 area on the surface of a pot to which 100 µL of each solution was applied and dried. Thus, there were 200 µg carbon in the sample at each application site.

Table I: Substances used for residue measurements.

Substance name	Solubility in water	Solvent use in solution preparation
Tranexamic acid	Soluble	Water
Anhydrous caffeine	Soluble	Water
Isopropylantipyrine	Insoluble	Ethanol
Nifedipine	Insoluble	Acetone
Gentashin ointment	Very insoluble	Ethanol
Rinderon ointment	Very insoluble	Acetone

Table II: Measurements using rinse sampling.

Substance name	TOC concentration (mgC/L)	Recovery rate (%)	Coefficient of variation (%)
Blank	0.030	-	-
Tranexamic acid	2.14	105	1.26
Anhydrous caffeine	2.19	108	1.86
Isopropylantipyrine	2.20	109	1.97
Nifedipine	2.17	107	1.97
Gentashin ointment	0.117	4.35	16.73
Rinderon ointment	0.333	15.2	58.60

Rinse-sampling method

In rinse sampling, the final rinse water from the cleaning of a production-equipment unit is used as the TOC measurement sample. This method is suitable for systems that cannot easily be disassembled, such as clean-in-place (CIP) equipment and narrow tubing. Sampling is considered to be difficult if the residues are not soluble in water.

To evaluate recovery of the various substances using this method, 100 mL of pure water was stirred for 15 min in the stainless steel pot that contained a patch of dried sample. TOC measurement was conducted on the rinse solution using a TOC analyzer (TOC-LCPH, Shimadzu) with a high-sensitivity catalyst. The analysis of TOC was by acidify and sparge method. The calibration curve was a 2-point curve using 0–3 mgC/L potassium hydrogen phthalate aqueous solution. A 500-µL injection volume was used. Because the carbon content in each of the residue measurement samples was 200 µg, the theoretical TOC concentration (i.e., if all carbon were to dissolve in rinse water) would be 2 mgC/L. **Figure 1** shows the measured TOC concentrations for representatives of water-soluble samples (a, tranexamic acid), water-insoluble samples (b, isopropylantipyrine), and water-insoluble ointments (c, Gentashin ointment). The other samples (i.e., anhydrous caffeine, nifedipine, and Rinderon ointment) have similar profiles to the samples with corresponding solubility.

For the blank, measurement was conducted in the same way using water in a stainless steel pot without dried sample applied to its surface. The measured blank concentration was subtracted from each TOC concentration and divided by the theoretical value of 2 mgC/L (i.e., the theoretical concentration if all of the sample were to dissolve in the water) to determine the rate of recovery, as shown in **Equation 1**.

$$\text{Recovery Rate (\%)} = \left(\frac{TOC_{Substance} - TOC_{Blank}}{TOC_{Theoretical}} \right) \times 100 \qquad \text{Eq. 1}$$

All samples were run in triplicate, and the coefficient of variation values (CV) are shown in **Table II** along with the TOC concentrations and the recovery rates.

Figure 1: Total organic carbon (TOC) concentrations for (a) tranexamic acid, (b) isopropylantirine, and (c) Gentashin ointment using rinse sampling.

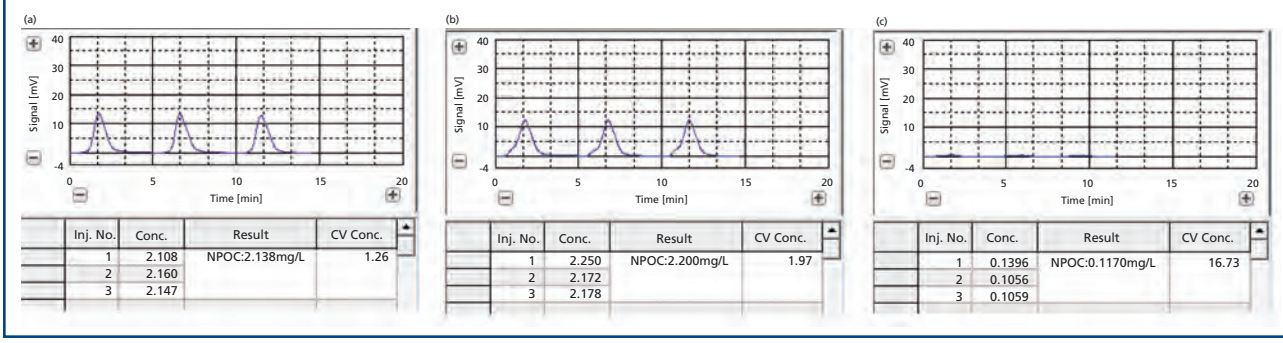

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Figure 2: Total organic carbon (TOC) concentrations for (a) tranexamic acid, (b)isopropylantirine, and (c) Gentashin ointment using swab sampling with water extraction.

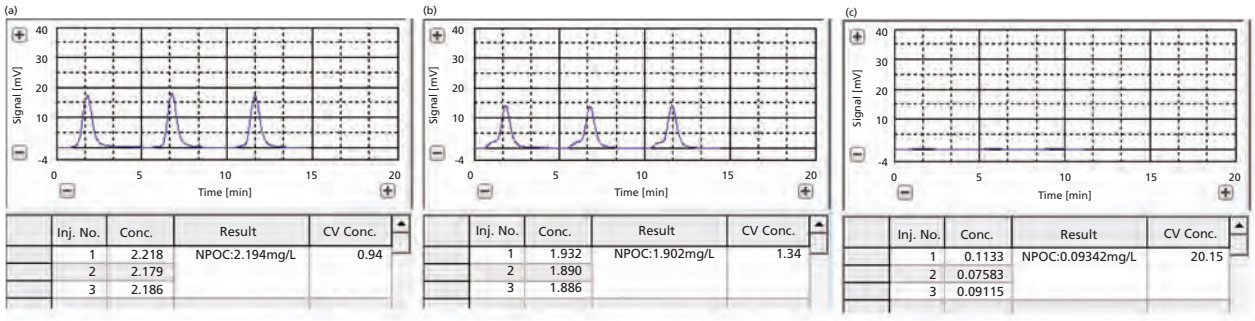

Table III: Measurements using swab sampling with water extraction.

Substance name	TOC concentration (mgC/L)	Recovery rate (%)	Coefficient of variation (%)
Blank	0.059	-	-
Tranexamic acid	2.19	107	0.94
Anhydrous caffeine	2.23	109	0.91
Isopropylantipyrine	1.90	92.2	1.34
Nifedipine	1.86	89.9	0.36
Gentashin ointment	0.093	1.70	20.15
Rinderon ointment	0.208	7.45	10.72

Water-soluble tranexamic acid and water-insoluble anhydrous caffeine had high recovery rates, as expected. Moreover, water-insoluble isopropylantipyrine and nifedipine had high recovery rates. However, recovery rates of Gentashin ointment and Rinderon ointment were both low, at less than 20%. Consequently, the TOC rinse method, while acceptable for some substances, is unsuitable for ointments and other similar substances.

Swab-sampling with water-extraction method

Swab sampling with water extraction consists of wiping the inside surface of the production apparatus with a fibrous swab material, extracting the adhering material with water, and conducting TOC measurement of the extract solution. Since the residue is physically wiped off from a fixed area of the surface, sampling efficiency is high. Residues that are insoluble in water, however, are difficult to extract with water. Accordingly, evaluating water-insoluble residues with this method may present similar difficulties to the rinse-sampling method.

To evaluate the recovery of the various substances using swab sampling with water extraction, the sample applied to the stainless-steel pot was wiped off with a 5-cm^2 piece of fibrous swab material, which was placed in a glass jar containing 100 mL of pure water. The fibrous swab material (Texwipe Alpha 10 swab washed in pure water and dried) consists of polyester so that very little organic material is extracted from the swab itself. The residue was extracted by stirring for 1 h, and TOC measurement was conducted using the same equipment and conditions used for the rinse-sampling method. Three replicates of each sample were run. As in the rinse-sampling method, because the carbon content in each of the residue measurement samples is 200 µg, the TOC concentration (i.e., theoretical TOC) in the extraction solution would be 2 mgC/L if all of the sample were wiped off. Representative data are shown in **Figure 2**. For the blank, measurement was conducted in the same way by wiping the stainless pot, which had no sample applied before conducting extraction. Recovery rate was determined using **Equation 1**. The results are shown in **Table III**.

Water-soluble tranexamic acid and anhydrous caffeine had high recovery rates as expected. Moreover, water-insoluble isopropylantipyrine and nifedipine had high recovery rates of approximately 90%. However, recovery rates of Gentashin ointment and Rinderon ointment were both low, at less than 10%. These results show that the TOC water-extraction rinse method is reliable and accurate for some substances, but unsuitable for ointments and perhaps other such substances due to the low recovery rates.

Swab-sampling with direct-combustion method

Swab sampling with direct combustion consists of wiping the inside surface of the production apparatus with a piece of quartz filter-paper swab material, and then conducting measurement using a direct-combustion carbon-measurement system. The swab material with adhering residue is measured directly (i.e., without first extracting with water) in a TOC analyzer using a connected solid-sample combustion unit or module (SSM).

To evaluate the rate of recovery of the different types of substances using this method, paper swab material (45-mm diameter Advantec quartz glass paper QR-100, heat treated at 600 °C for 15 min) was used to wipe the sample adhering to the stainless steel pot and placed in the sample boat, which is then placed in the SSM (SSM-5000A, Shimadzu)

Figure 3: Total organic carbon (TOC) concentrations for (a) tranexamic acid, (b) isopropylantirine, and (c) Gentashin ointment using swab sampling with direct combustion.

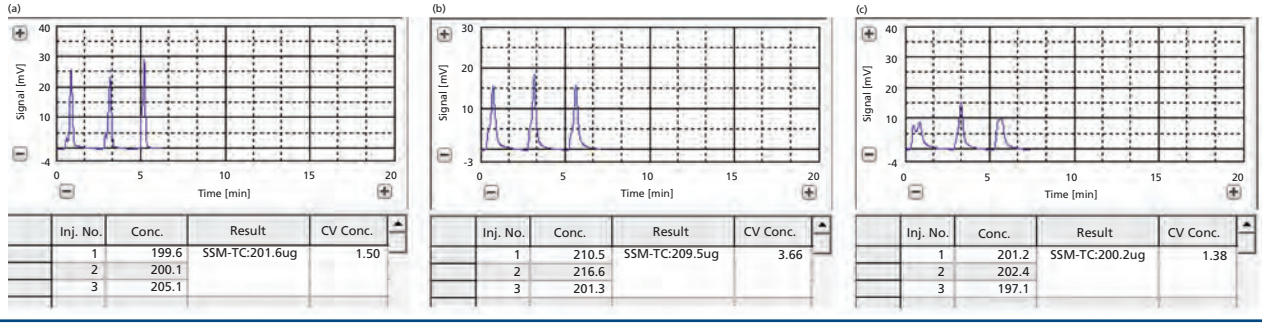

Table IV: Measurements using swab sampling with direct combustion.

Substance name	TOC value [µC]	Recovery rate (%)	Coefficient of variation (%)
Blank	0.00	-	-
Tranexamic acid	202	101	1.50
Anhydrous caffeine	201	100	2.43
Isopropylantipyrine	210	105	3.66
Nifedipine	212	106	0.80
Gentashin ointment	200	100	1.38
Rinderon ointment	209	104	1.31

Table V: Summary of measurement results.

		Recovery rate (%)		
Substance name	Solubility in water	Rinse sampling	Swab sampling with water extraction	Swab sampling with direct combustion
Tranexamic acid	Soluble	105	107	101
Anhydrous caffeine	Soluble	108	109	100
Isopropylantipyrine	Insoluble	109	92.2	105
Nifedipine	Insoluble	107	89.9	106
Gentashin ointment	Insoluble	4.35	1.70	100
Rinderon ointment	Insoluble	15.2	7.45	104

connected to the TOC analyzer (TOC-LCPH, Shimadzu). Three replicates of each sample were run. The SSM uses 400 mL/min oxygen as a carrier gas. The calibration curve is a 1-point calibration using 1% C glucose aqueous solution. The total carbon (TC) content on the swab was measured directly by the TOC analyzer. Selected measurement data are shown in **Figure 3**.

Since the carbon content in each of the residue measurement samples is 200 µg, the TC value would be 200 µg if all of the sample were wiped off. For the blank, measurement was conducted in the same way by wiping the stainless pot, which had no sample applied. The measured blank value was subtracted from each TC value, and then divided by the theoretical value of 200 µg using **Equation 1** to determine the rate of recovery. The results are shown in **Table IV**. A high recovery rate of about 100% was obtained for all the substances, regardless of whether they were water soluble or water insoluble.

Conclusion

The measurement methods used here and their respective recovery rates are summarized in **Table V**. When using the rinse- and swab-sampling methods, some of the water-insoluble substances had high recovery rates while others had low recovery rates. It is thought that this may be due to differences in the affinity with which the substances adhere to the stainless steel pot. Accordingly, it is possible that residue evaluation using these methods would be difficult for substances with low recovery rates.

In contrast, high recovery rates were obtained for all the substances when using the swab sampling with direct-combustion method, regardless of whether the substances were water soluble or water insoluble. Therefore, this method is considered to be the most versatile measurement method for conducting cleaning validation, especially when multiple compounds are being manufactured in the same vat, if the compounds are unknown, or if there is a possibility the known compounds will decompose into other compounds.

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What would you do differently? Email your thoughts about this paper to ptweb@advanstar.com and we may post them on PharmTech.com.

Early Development GMPs for Drug-Product Manufacturing of Small Molecules

An Industry Perspective (Part III)

Richard Creekmore, Eleni Dokou, Amnon Eylath, Dennis Joiner, Michael Lovdahl, Jackson Pellett, Eric Schmitt, and John W. Skoug

The authors, part of the International Consortium on Innovation and Quality in Pharmaceutical Development (IQ Consortium), explore and define common industry approaches and practices when applying GMPs in early development. A working group of the consortium aims to develop a set of recommendations that can help the industry identify opportunities to improve lead time to first-in-human studies and reduce development costs while maintaining required quality standards and ensuring patient safety. This article is the third paper in the series and focuses on drug-product manufacturing.

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The International Consortium on Innovation and Quality in Pharmaceutical Development (IQ) formed in 2010, and is an association of more than 25 pharmaceutical and biotechnology companies with a mission to advance science-based and scientifically driven standards and regulations for medicinal products worldwide. In the June 2012 issue of *Pharmaceutical Technology*, a paper written by the IQ Consortium's GMPs in Early Development Working Group described the desire and rationale for more clear and consolidated recommendations for GMPs in early development (Phase 1 through Phase 2a) (1). A consequence of the absence of clarity surrounding early phase GMP guidances has been varied interpretation and application of existing GMP guidances within different companies according to its own culture and risk tolerance. Internal debates often result in conservative "one-size-fits-all" interpretations that rely on International Conference on Harmonization (ICH) guidelines that are mostly relevant to commercial product development and do not distinguish differences in requirements between early development and later stage development (Phase 2b and beyond). A key driver of this working group (WG), therefore, has been to collectively define the minimum acceptable practices within the industry regarding GMP expectations in early development that allow for added flexibility, are consistent with existing guidance and statutes, and which assure product quality and patient safety (2–4).

The second paper in this series addressed recommendations for analytical method validation of both drug substances (DS) and drug products (DP) (5). In this third article of the series, the authors address the application of GMPs in early development as they pertain to drug-product manufacturing.

Background

As noted previously in the introduction to the paper series, due to high attrition in early development, most companies try to minimize the resource required to advance compounds into human clinical trials by employing simple formulations and manufacturing processes (1). For example, drug substance filled in bottle,

Table I. Survey results of IQ member companies related to drug-product manufacturing in early development. A total of 10 companies responded.

	% Response		
Question	**Never**	**Sometimes**	**Routinely**
In early development, does your company manufacture GMP clinical trial supplies (CTS) prior to full release of the API?	40%	50%	10%
In early development, does your company manufacture CTS prior to completion of full release testing of excipients?	40%	30%	30%
In early development, does your company repeat vendor testing for excipients used in CTS manufactures?	10%	70%	20%
Question	**Yes**	**No**	
In early development, does your company require a vendor laboratory audit to accept materials on vendor CoA?	30%**	40%	
Does the quality unit pre-approve CTS batch records?	100%	0%	
Do you feel your company's approach to handle deviations that occur during early development CTS manufacturing provides adequate flexibility?	60%	40%	
Is a corrective and preventive action (CAPA) program applied to all early phase manufacturing exceptions?	55%	45%	
Are the quality system/requirements for R&D different than what is used in commercial production?	90%	10%	
Are the quality system/requirements for early development CTS different than later stage (Phase 2b and beyond) development?	50%	50%	
** The remaining 30% indicated their company does not allow acceptance of materials based on vendor COA.			

drug in capsule, or simple powder blends filled in capsule are frequently used. Even for more challenging molecules, for example, those with low aqueous solubility, prototype formulations designed to investigate bioavailability enhancement (e.g., amorphous solid dispersions, lipid-based drug delivery systems, nanosuspensions) are evaluated in as simple a manner as possible. For example, on-site preparation at the clinic site of an amorphous solid dispersion by weighing into a capsule, or by suspension in a suitable vehicle may be utilized instead of a finished tablet or capsule dosage form. Whatever approach to formulation/process is taken, there is a need for flexibility in manufacturing due to limited product and process understanding in early development.

Based on the collective industry experience of the members of this working group, the authors believe that pharmaceutical companies could be making better use of available guidances as they pertain to drug-product manufacturing in early development. This belief was reflected by the mixed responses to a survey of IQ member companies conducted in late 2011 (see **Table I**). Accordingly, in this article, the authors provide pragmatic recommendations related to GMP drug-product manufacturing focusing on those areas where it is believed there is opportunity for added clarity and flexibility, without added risk to product quality and patient safety.

Following a brief explanation of the role and importance of quality systems, the areas highlighted in this paper include facilities, equipment, materials (receipt and approval for use), and batch documentation. Not covered is cleaning verification/validation, as this is a topic that is addressed in detail in the industry (6). The scope of this position paper has purposely been limited to traditional small molecules that are formulated into solid oral dosage forms intended for US regulatory filings with the desire to build consistency across all worldwide regulatory regions. However, it is believed that the concepts presented can be easily adapted to other dosage forms and routes of administration. Although designed as an industry position, it is recognized that each company needs to evaluate these recommendations for drug-product manufacturing practices based on individual business needs and risk culture.

Quality systems

GMP quality system. In early development, relationships between material attributes, process parameters and product quality attributes are typically not well understood. It should be anticipated that even during GMP manufacture, there will likely be a need to deviate from the process conditions specified in a batch record. Quality systems should have the flexibility to allow these changes to be documented in batch records without formal prior approval from the Quality department. However, these changes should be reviewed by Quality after production, to assess the potential impact to product quality and patient safety. It is crucial to summarize and track process changes because much of this information will be used to develop process understanding and may be included in development history reports. In a similar manner, unplanned deviations from the written manufacturing procedures should be documented and justified, but may not need to be addressed in a formal corrective and preventive action (CAPA) system, because the process is changing continuously as part of the development

process. Unplanned deviations that are likely to impact product quality and patient safety, such as cleaning failures, contaminations, and certain equipment failures must be investigated and corrective actions put in place to prevent recurrence.

Risk management in early development. To assist in the application of risk-based decision making in the development and manufacturing of drug product, the authors recommend that companies apply a scientific and risk-based approach, similar in principle to that of the ICH Q9 *Quality Risk Management* guideline (7). Annex I of the guideline describes various methods and tools that can be useful to determine the relative risks related to system risks, such as facility and people; organizations (including quality systems); process risks and product risks (safety and efficacy). There are many ways of identifying, qualifying, and mitigating operational and quality risks. Regardless of the methodology used, a documented strategy and good records of risk-based decisions are important in ensuring that the appropriate factors are considered for the protection of patients and product quality.

Facilities and equipment

Regardless of the scale of manufacturing, the facility used for manufacturing clinical trial supplies must meet the basic GMP requirements as described in the regulations and guidance documents. Below are three scenarios for early development and the advantages of each as pertaining to early development. The first involves a pilot plant facility designed and equipped for routine GMP operations. The second scenario aims to establish a GMP area within a laboratory environment. The third example focuses on conducting GMP manufacturing or leveraging the practice of pharmacy in close proximity to the clinical site.

GMP facility for drug-product manufacture. The traditional approach in GMP drug-product manufacture is to use a dedicated facility (often called a pilot plant) for early phase clinical trials. Advantages of this approach include that the quality systems for the facility (i.e., maintenance, calibration, cleaning, change management, CAPA, and documentation) are well defined, and that training and other activities required for maintaining GMP compliance are centralized. Other drivers to use a pilot plant in early development may be the need for specialized equipment, or larger batch sizes in special situations.

GMP area within a laboratory setting. In some cases, it may be advantageous to establish a GMP area within a "laboratory setting" (i.e., a drug-development facility not dedicated to the production of clinical supplies) for the manufacture of drug product in early development. The rationale for this approach might be to avoid the significant investment in setting up a dedicated facility and to create simpler, more flexible systems that meet GMP requirements but are tailored for the specific activity envisioned. Examples where this approach might be considered include the need for special containment not available in the pilot-plant; the need to work with radioactive or hazardous materials, use of controlled substances and the production of "one-off manufactured" product used for proof of concept. The business rationale should be documented and approved by the manufacturing and Quality groups. As long as the appropriate GMP controls are maintained, especially as related to operator safety, cleaning, and prevention of cross-contamination, there is no compliance barrier to using "lab-type" facilities for the manufacturing of early phase clinical batches. Before GMP manufacturing is initiated, however, a risk assessment should be conducted and documented. Inclusion of representatives from Quality, analytical, clinical manufacturing, product development, and environmental health and safety would be prudent. When selecting/designing an early development clinical manufacturing facility, consideration should be made for the receipt, storage, dispensing, and movement of materials. The manufacturing processes in the nondedicated area must protect the product, patient, and the manufacturing operators.

Additionally, companies should consider what items are appropriate for the manufacture. For example, the use of a certified laminar flow hood may be a better choice for manufacturing than a fume hood, because the former is designed to prevent contamination of the product, protect the operator, and the laboratory environment. In addition, with the appropriate cleaning, a laminar flow hood can more easily be used for multiple products. Small scale/manual equipment or procedures may be the best approach because the space is likely to be limited. With a small batch size, the use of small scale or manual equipment/procedures will minimize yield loss. Additional measures to be assessed include appropriate gowning and operator personal protection devices, area and operator monitoring for potent or radiolabeled drug exposure, and so forth.

Documentation of the facility preparation, product manufacture, and the return of the facility to the previous state, if needed, is recommended. This documentation should describe the rationale for the manufacture in the nondedicated area, risk assessment, preparation of the area, cleaning procedures, and list of responsible persons. This documentation can reference existing procedures or standard operating procedures (SOPs) along with documents associated with the meetings and preparation for the manufacture of the batch. Batch records and cleaning records should be part of the documentation and should follow the company's data-retention policy.

Preparation at the clinical site. On-site preparation of formulations, sometimes referred to as "extemporaneous preparation" or "compounding," is not considered manufacturing, but is an effective method to prepare early clinical supplies using the local laws governing the practice of pharmacy. The processes used for on-site preparation can be as simple as preparing and diluting solutions or filling capsules with API to more complicated processes such as blending and compression of tablets. An IQ working group addressing current practices in extemporaneous preparation has conducted a survey to be communicated at a later date, which confirms that only a few companies have adopted practices to take advantage of more advanced formulation approaches at the clinic site (8). This is a missed opportunity, because on-site preparation of formulations has the potential to dramatically speed industry's ability to answer critical questions related to pharmacokinetic parameters, absolute or relative bioavailability, feasibility of extended release and bioavailability enhancement approaches for difficult to deliver molecules. Currently, each company must develop its own

best practices to assure product quality and patient safety; often, these practices are based on compendial or professional association publications (9–11). The authors believe this topic warrants further discussion between the industry and regulatory authorities to determine when dose preparation at the clinical site is appropriate and the level of quality controls required. The results of such a discussion could help to increase the utilization of on-site preparation of clinical trial materials to facilitate quick answers to critical questions in early drug development and ultimately bring the best possible products to patients in the shortest time.

Equipment. Most equipment used to manufacture early GMP drug product is be managed under a qualification, preventive maintenance, and calibration program for the GMP facility. However, in early development, there may occasionally be a need to use equipment that is not part of such a program. Rather than performing a comprehensive qualification for a piece of equipment not expected to be frequently used, an organization may choose to qualify it for a single step or campaign. Documentation from an installation qualification/operational qualification (IQ/OQ) and or performance verification at the proposed operating condition is sufficient. For example, if solution preparation needs a mixer with a rotation speed of 75 rpm, then documentation in the batch record using a calibrated tachometer to verify that the mixer was operating at 75 rpm will suffice.

The use of dedicated or disposable equipment or product contact parts may be preferable to following standard cleaning procedures to ensure equipment is clean and acceptable for use. However, not all equipment or equipment parts are disposable or may have a substantial cost that makes disposal prohibitive. In that case, the product contact parts could be dedicated to a specific drug substance for use in drug product manufacture. Dedicating product contact parts to a compound may be costly and may be avoided in some cases by carefully considering product changeover and effective cleaning methods when purchasing equipment.

Another item to consider with respect to equipment, is that the more complicated the equipment is to run or maintain, the less desirable it might be for early GMP batches. In most cases, simple equipment is adequate and will uses less material and consume less total time for preparation, operation, and cleaning activities.

Raw materials

Buildings and facilities. GMPs under the 21 *Code of Federal Regulations (CFR)* Part 211.42 state that buildings or areas used in the receiving, storage, and handling of raw materials should be of suitable size, construction and location to allow for the proper cleaning, maintenance, and operation (7). The common theme for this section of *CFR* Parts 210 and 211 is the prevention of errors and contamination. In principle, the requirements for buildings and facilities used in early phase manufacturing are not significantly different than those for later phases or even commercial production. However, there are some areas that are unique to early clinical trial manufacturing.

Control of materials. The *CFR* regulations under Part 211.80 provide good direction with respect to lot identification, inventory, receipt, storage, and destruction of materials (7). The clear intent is to ensure patient safety by establishing controls that prevent errors or cross-contamination and ensure traceability of components from receipt through clinical use. In general, the requirements for the control of materials are identical across all phases of development, so it is important to consider these requirements when designing a GMP facility within a laboratory setting.

For example, all materials must be assigned a unique lot number and have proper labeling. An inventory system must provide for tracking each lot of each component with a record for each use. Upon receipt, each lot should be visually examined for appropriate labeling and for evidence of tampering or contamination. Materials should be placed into quarantine or in the approved area or reject area with proper labeling to identify the material and prevent mix-ups with other materials in the storage area. Provision should be made for materials with special storage requirements (e.g., refrigeration, high security). The storage labeling should match the actual conditions that the material is being stored and should include expiry/retest dates for approved materials. Although such labeling is inconvenient for new materials where the expiration or retest date may change as more information is known, this enables personnel to be able to determine quickly whether a particular lot of a material is nearing or exceeding the expiration or retest date. General expiry/retest dates for common materials should be based on manufacturer's recommendation or the literature.

Finally, there are clear regulatory and environmental requirements for the destruction of expired or rejected materials. It is important to observe regional and international requirements regarding the use of animal sourced materials (12). It is recommended to use materials that are not animal sourced and that there be available certification by the raw material manufacturers that they contain no animal sourced materials. If animal sourced raw materials must be used, then certifications by the raw material manufacturers that they either originate from certified and approved (by regulatory bodies) sources for use in human pharmaceuticals, or that the material has been tested to the level required for acceptance by regulatory agencies (following US, EU, or Japanese guidelines, as applicable) is required.

Receipt and approval

Specifications. It is a GMP requirement that all raw materials for the manufacture of drug product have appropriate specifications to ensure quality. The compendial requirements should be used for setting specifications provided the material is listed in at least one pharmaceutical compendium (e.g., *US, European,* and *Japanese Pharmacopeias*). It is important that the use of materials meeting the requirements of a single compendium is acceptable for use in early phase clinical studies conducted in the US, Europe, and Japan. For example, a material that meets *USP* criteria and is used in the manufacture of a drug product should be acceptable for use in early clinical studies in the European Union. In the absence of a pharmaceutical compendium monograph, the vendor specification and/or alternative compendial specifications such as USP's Food Chemical Codex should guide specification setting. In any case, the sponsor is responsible for the establishment of appropriate specifications. Therefore, it is the authors' position that good prac-

tice is to have at least a basic understanding of the manufacture, chemistry, and toxicology of the materials to guide appropriate specification setting.

Material testing and evaluation. The minimum testing required for incoming materials is visual inspection and identification. However, as mentioned above, the appropriate tests should be determined for the material based on the knowledge of the manufacture, chemistry, and toxicology. If the vendor is qualified, then the certificate of analysis may be acceptable in conjunction with the visual inspection and identification testing (see "Vendor Qualification" section below).

Approval for use. Ideally, manufacture of a bulk drug product should begin with approved material specifications and with materials that are fully tested and released. However, there are circumstances where it may not be feasible to start manufacture with approved specifications and fully tested and released materials, including API. Manufacturing prior to final release (sometimes called manufacturing "at risk") may be acceptable, however, because the quality system ensures that all specifications are approved, test results are within specifications, and all relevant documents are in place before the product is released for administration to humans. The "risk" must lie fully with the manufacturer and not with the patient.

Vendor qualification. Vendors supplying excipients, raw materials, or API must be qualified by the sponsor. Appropriate qualification should depend on the stage of development and an internal risk assessment. For, example if a vendor has a history of supplying the pharmaceutical industry and the material is to be used in early development, a paper assessment (e.g., a questionnaire) should be sufficient. If a supplier does not have a history of supplying the pharmaceutical industry, a risk assessment should be performed and depending on the outcome a site audit may be required prior to accepting material for use.

Ideally, vendors should be qualified prior to using raw materials for manufacture. However, it is acceptable for qualification to proceed in parallel as long as documentation/risk assessments are available prior to product release and as in the previous section all risk lies with the manufacturer and not the patient.

Batch documentation and execution

Batch record documentation preparation. Manufacturing documentation is a basic requirement for all phases of clinical development. 21 *CFR* Parts 211.186 and 211.188 describe master production and batch production records, respectively (7). The stated purpose of the master production record is to "assure uniformity from batch to batch." Although the record assurance is important for a commercial validated manufacturing process, it does not necessarily apply to clinical-development batches. Material properties, manufacturing scale, and quality target product profile frequently change from batch to batch. Therefore, batch production records are the appropriate documentation for clinical trial supplies. Batch production records for Phase 1 materials should minimally include:

- Name, strength, and description of the dosage form
- A complete list of active and inactive ingredients, including weight or measure per dosage unit and total weight or measure per unit
- Theoretical batch size (number of units)
- Manufacturing and control instructions.

These minimum requirements are consistent with the FDA *Guidance for Industry: cGMP for Early Phase Investigational Drugs,* which requires a record of manufacturing that details the materials, equipment, procedures used and any problems encountered during manufacturing (2). The records should allow for the replication of the process. On this basis, there is flexibility in the manner for which documentation of batch activities can occur, provided that the documentation allows for the post execution review by the quality unit and for the retention of these records.

Batch documentation approvals. Review and approval of executed batch records by the Quality unit is required per 21 *CFR* Part 211.192 (7). This review and approval is required for all stages of clinical manufacturing. Pre-approvals of batch records should be governed by internal procedures as there is no requirement in *CFR* 21 that the Quality unit pre-approves the batch record (though this is highly recommended in order to minimize the chance of errors). Indeed, **Table I** shows that pre-approval of batch records by the Quality Unit is practiced by all 10 companies that participated in the IQ Consortium's drug-product manufacturing survey related to early development. Batch records must be retained for at least 1 year after the expiration of the batch according to CFR Part 211.180, but many companies keep their GMP records archived for longer terms.

Room clearance. 21 *CFR* Part 211.130 requires inspection of packaging and labeling facilities immediately before use to ensure that all drug products from previous operations have been removed. This inspection should be documented and can be performed by any qualified individual.

Although line clearance for bulk manufacture is not specifically mentioned in the *CFR*, it is expected that a room clearance be performed. At a minimum, this clearance should be performed prior to the initiation of a new batch (i.e., prior to batch materials entering a processing room).

Hold time. During the early stages of development, final dosage form release testing confirms product quality and support establishment of hold times later in the clinical development. There is no requirement to establish hold times for work in process in early development. Specific formulation and stability experience, which is usually limited at this stage of development, should be leveraged to assess any substantial variations from expected batch processing times. The data gathered from these batches and subsequent development can be used to help establish hold times for future batches. (Exceptions to this approach may include solution or suspension preparations used in solid dosage form manufacturing, where procedures typically govern allowable hold times to ensure the absence of microbial contamination in the final product.)

Change control. Changes to raw materials, processes, and products during early development are inevitable. It is not required that these changes be controlled by a central system but

rather may be appropriately documented in technical reports and manufacturing batch records. Any changes in manufacturing process from a previous batch should be captured as part of the batch record documentation and communicated to affected areas. The rationale for these changes should also be documented as this serves as a source for development history reports and for updating regulatory filings. The authors recommend that those changes that could affect a regulatory filing be captured in a formal system.

Process changes. Process parameters should be recorded but do not need to be predetermined because processes may not be fixed or established in early development. Given the limited API availability in early development, a clinical batch is often the first time a product is manufactured at a particular scale or using a particular process train. Therefore, process changes should be expected. Process trains and operating parameters must be documented in the batch record but changes should not trigger an exception report or CAPA. Changes should be documented as an operational note or modification to the batch record in real time. Such changes driven by technical observations should not require prior approval by the Quality unit, but should have the appropriate scientific justification (*via* formulator/scientist) or the appropriate flexibility built into the batch record to allow for the changes. This documentation should be available for Quality review prior to product disposition.

Calculation of yield. Actual yields should be calculated for major processing steps to further process understanding and enable optimization of processes. Expected yield tolerances are not always applicable to early development manufacture. At this stage of early development, when formulation and process knowledge is extremely limited, there may be no technical basis for setting yield tolerances and, therefore, this yield may not be an indicator of the quality of the final product.

In-process controls and R&D sampling. In-process tests and controls should follow basic requirements of GMPS to document consistency of the batch. For capsule products, these requirements may include capsule weights and physical inspection. For tablet products, compression force or tablet hardness and weights should be monitored together with appearance. R&D sampling, defined as samples taken for purposes of furthering process understanding but not utilized for batch disposition decisions, is a normal part of all phases of clinical manufacturing. In early development manufacturing, a sampling plan is required for in-process control tests, but not for R&D samples. However, for the purpose of material accountability, R&D sampling should be documented as part of batch execution. For these samples, testing results may be managed separately, and are not required to be included in regulatory documentation.

Conclusion

Organizations involved in manufacture of Phase 1 and 2a clinical supplies should recognize that process understanding is very limited in early development. Quality systems must be robust enough to ensure patient safety, but should also be flexible enough to accommodate accelerated timelines and process changes in real time. The special needs of small scale GMP manufacturing should also be considered when designing facilities, purchasing equipment, and selecting the type of dosage forms to use in early clinical studies. Companies are encouraged to apply quality risk management principles to support these risk-based decisions.

The authors also believe that underutilized approaches exist (e.g., on-site preparation of more complex dosage forms) for quickly and efficiently answering formulation related questions about bioavailability, pharmacokinetics, and target release rates for controlled-release formulations. The potential benefits and risks of these approaches warrant further discussion. Finally, documentation of manufacturing operations should be risk-based. Manufacturing instructions in early development should not be overly prescriptive as to restrict process changes or discourage sampling for further process understanding. Changes should be expected, and able to be quickly reviewed and approved by the Quality department, or a qualified delegate.

To further stimulate discussions on these approaches within the industry and with worldwide health authorities, the IQ Consortium's GMPs in Early Development Working Group is planning on conducting a workshop in the near future to promote robust debate and discussion on these recommended approaches to GMPs in early development. The group strongly believes that such dialogue will improve alignment between development, quality assurance, and chemistry/manufacturing/controls (CMC) regulatory groups within the pharmaceutical industry. In addition, agreement between the industry and drug regulatory authorities regarding acceptable approaches to applying GMPs in early phases of drug development would allow for a more nimble and flexible approach in early development, while still providing appropriate controls to ensure patient safety.

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Elemental Impurity Analysis

How to Manage the Pharmacopeial Changes Ahead

Alan Cross

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The United States Pharmacopeia (USP) has revised its elemental impurities limits and procedureal chapters with implementation set for May 2014. The author explains the need for these revisions and provides a look at some of USP's proposed techniques for elemental impurity detection and identification.

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Revisions to *US Pharmacopeia* General Chapter <231> Heavy Metals have been mooted and proposed for more than a decade, and it has long been known that the current methods are highly subjective and likely to prove inaccurate, at least for certain metals. The road to reform has been somewhat stuttering, but after a long period of review and commentary, on Dec. 1, 2012, General Chapter <232> Elemental Impurities—Limits and Chapter <233> Elemental Impurities—Procedures will be published in the second supplement of the *US Pharmacopeia* 35–*National Forumulary* 30 (*USP–NF*).

On May 1, 2014, when *USP* 37–*NF* 32 becomes official, all references to Chapter <231> will cease to exist, and conformance to Chapter <232> and Chapter <233> within the General Notices will be required. The acceptance of these chapters will open the door for laboratories to use a wider range of methods for analyzing heavy metal contaminants. Of course, these methods will still need to be validated, and there may still be room for debate about which methods are best for any given situation, but at least the dubious methods of Chapter <231> will cease to be available for medicines marketed in the United States. (For the time being, the comparable methods used in the European and Japanese pharmacopoeias will continue to be available.) This paper addresses the need for new compendial requirements, with a focus on elemental impurity detection and identification.

The need for change

Testing for heavy metals is actually one of the most established ideas contained within the national pharmacopeias around the world. In fact, USP has included a general test for heavy metals since 1905 in the eighth volume of the pharmacopeia, which used sulphide precipitation to detect antimony, arsenic, cadmium, copper, iron, lead, and zinc. As it happens, the purpose of the test had more to do with prevention of mislabeling than prevention of contamination, because heavy metal salts were often used in therapy and one had to know which salts were present in a treatment. The need to detect residual contamination was established in 1942, with the introduction of *USP* volume XII, in which a lead-containing standard was included in the test. The goal was to detect potentially poisonous heavy metal residuals,

such as lead and copper, because these metals were widely used in production equipment at the time. Interestingly, metals such as iron, chromium, and nickel were not revealed by the test (1). Ultimately, it is the inapplicability of a "standard" test (such as that defined by Chapter <231>) that has led to its demise and the need for more flexibility.

Industry knowledge of common metal contaminants. Metal impurities are rightly a cause for concern in pharmaceutical products and there are many means by which a product might become contaminated. There are many inorganic impurities that are deliberately added to the pharmaceutical processes (e.g., catalysts). There are other impurities that can arise as undetected contaminants from starting materials or reagents, or that come from the process itself (e.g., leaching from pipes and other equipment). Then, of course, there are metal ions that occur naturally within the plant or mineral sources that are used to produce the active ingredients of pharmaceuticals and herbal medicines.

Regardless of how metals may get into a product, or previous certification of these metals, pharmaceutical producers must carry out tests to demonstrate the absence of impurities before using materials in a pharmaceutical product.

General Chapter <232>: New limits

USP General Chapter <232> Elemental Impurities—Limits sets out the acceptable levels of 15 elements in final drug products. These limits have been evaluated from toxicological data and are expressed in terms of a daily permissible exposure (DPE) limit. The DPE also takes into consideration the route of administration (e.g., oral, parenteral, or inhalable) with orally administered drugs having a higher permissible limit than parenteral or inhaled drug products. Where elements on the list are known to be present or have the potential to be present then compliance with the specifications must be assessed. The 15 elements addressed in Chapter <232> are based on the International Conference on Harmonization's (ICH) Q3D Elemental Impurities Working Group pre-Stage 2 draft guideline (2).

Chapter <232> covers arsenic, cadmium, mercury, and lead—all elements that are considered ubiquitous and therefore must be assessed in all cases. In addition, the chapter covers iridium, osmium, palladium, platinum, rhodium, ruthenium, chromium, molybdenum, and nickel. The second group of elements may be present in products as a result of being added deliberately, for instance, in the form of a catalyst or through interactions with metal components through the manufacturing process.

Because the ICH Q3D guideline is still being reviewed and is likely to expand to cover more elements, it has been decided that a review of Chapter <232> will happen after the deliberations on ICH Q3D guidelines have been completed. At this stage, the scope of Chapter <232> may be expanded to cover more elements, or an informational chapter may be incorporated to cover elements of low toxicity.

The outdating of long-standing tests

It is fair to point out that the methods of *USP* General Chapter <231> were developed before the introduction of modern analytical instruments. These methods were easily transferable from one laboratory to another and did not require sophisticated instrumentation or specialized expertise. Hence, a competent laboratory staff member could perform the same techniques with relative ease. The problem was that the methods themselves were flawed, no matter how competent the analyst.

For example, Chapter <231> methods involved subjective visual examination and comparison of the sample solution with a lead standard. Similar to the method of 1905, the compendial methods used a reaction to form the sulphide of any metal ions present and the total metal content was reported against the lead standard response as a limit test.

The validity of this comparison relied on several assumptions, all of which can be questioned. For example, the compendial method assumed that each of the heavy metals in the sample matrix would react in a like manner to lead to form a sulphide species. This assumption applied despite many sulphides being known to be insoluble and despite some elements being known to have a far more intensely colored sulphide than the lead standard against which it was being assessed. Similarly, the compendial method assumed that the reaction kinetics for lead sulphide would be very similar to that of the other metal sulphides and that reaction kinetics were not greatly affected by the sample matrix. A final major and unsafe assumption was that the heating and/or ashing step of the method would have no impact on volatile metals (3).

Work has been carried out that suggests that recovery of mercury can be as little as 2% using the <231> compendial method, which clearly introduces a massive error in the final result (2). Other laboratories have reported similar poor recovery of metals such as tin, selenium, and antimony. These examples are by no means the only reasons to challenge the validity, applicability, and reliability of the compendial methods. In fact, additional chapters for the control of specific metals and other inorganic impurities have been added to *USP* over the years. Significant among these additions has been *USP* Chapter <730> Plasma Spectrochemistry, which gave laboratories the opportunity to use techniques such as inductively coupled plasma with either mass spectrometry or atomic emission spectroscopy (ICP–MS and ICP–AES).

The advantage of ICP methods is that they can provide specific detection and quantification for each of the elements specified in Chapter <232>. The subjectivity of the semiquantitative comparison that is required by the compendial methods is eliminated with ICP. The ICP techniques are also quicker in most cases, requiring a smaller sample size and giving a better detection limit for all the elements of interest. The sample preparation method for ICP, for example, is less likely to lead to the loss of the volatile elements.

Chapter <233>: New techniques

USP General Chapter <233> Elemental Impurities—Procedures sets out the general conditions for testing, covering preparation, analysis, and the parameters for validation. The preparation methods referred to above are neat, direct aqueous solution, direct organic solution and indirect solution.

Neat samples are in such a state that they can be used without further preparation. More commonly used solutions will need to

be prepared prior to analysis, and the simplest of these procedures is preparation of a direct solution whereby a product is dissolved or diluted with water/dilute acid or an organic solvent to give a solution for analysis.

In many cases, it may be desirable to treat the sample by breaking down any organic material contained within it; such a step typically reduces the ffect of the matrix effect which might otherwise give rise to false positive/negative results. If a sample is prepared in this way, then it is referred to as an indirect solution. These solutions are generally prepared using a microwave digester. In this technique, a small amount of sample is weighed into a vessel and acid is added. The vessel is sealed and placed into a microwave. In the microwave, the sample is heated to temperatures of up to 250 °C and pressures of up to 55 bar. Under these conditions, the sample matrix is effectively destroyed and the metal atoms are released into solution. After the sample is cooled, it is made up to a suitable volume with water ready for analysis.

ICP–MS and ICP–AES. As noted above, Chapter <233> sets out two procedures for analysis, ICP–MS and ICP–AES. The latter is also sometimes referred to as ICP–OES, which stands for optical emission spectrometry. In this technique, the sample solution is fed into an argon plasma which has a temperature of approximately 10,000 °C. The sample matrix is destroyed under these conditions, and individual atoms are released. These atoms are then excited to a higher energy state. As the excited atoms cool, they return to a "ground state." The process releases energy in the form of light, the wavelength of which is specific to a particular element. When this light falls on a detector, it can be quantitated and the amount of analyte can be evaluated.

ICP–MS is the second procedure specified in Chapter <223>. This technique also uses a plasma, but with this technique, the plasma is used to ionize the metal atoms which are then fed into a quadrapole which separates the ions according to their mass-to-charge ratio. Following separation, the ions fall onto a detector and the sample can be quantified.

Differentiating the new techniques. Both ICP–AES and ICP–MS are able to analyze several elements simultaneously. As a result, sample throughput can be very quick, typically 2–3 minutes per sample. Generally, it is fair to say that ICP–AES instrumentation is cheaper than ICP–MS, but both instruments have relatively high running costs due to the consumption of argon in the plasma. The key difference between the instruments is the detection limit. The ICP–MS typically has detection limits 100–10,000 times lower than that of ICP–AES. Both techniques are capable of analyzing to the levels required by USP, but ICP–MS can offer a much lower detection limit. Chapter <233> states that for both techniques, steps can be taken to remove matrix interferences. For ICP–AES, these interferences can occur from overlapping wavelengths. In this case, alternative wavelengths can be used for analysis. Also, many instrument manufacturers have correction techniques built into the operating software.

In the case of ICP–MS, the sources of matrix interferences come from the fact that different species can have the same mass/charge ratio. For example, argon chloride appears at the same mass as arsenic, giving false positive results. To remove these interferences, many instrument manufactures use special cells within the instrument that can add gases to the ions and mitigate the interferences.

Alternative methods

Other techniques can be used in the analysis of elemental impurities, but each must be validated to ensure that it is suitable and able to detect the analytes at the required level. Below are a few options:

Flame atomic absorption spectrometry (FAAS): This simple and relatively cheap technique has relatively high detection limits, especially for elements such as mercury and arsenic. FAAS can only analyze one element at a time.

Vapor generation atomic absorption spectrometry (VG–AAS): This technique involves a chemical reaction to release metals in the form of gaseous hydrides. It has improved detection limits compared with FAAS but can only be used for arsenic, bismuth, germanium, lead, antimony, selenium, tin, and tellurium. Only one element can be analyzed at a time. Reagents are used to generate the hydride therefore generating a higher cost than traditional AAS.

Graphite furnace atomic absorption spectrometry (GFAAS): In this technique, a small amount of sample is slowly heated to first dry then ash the sample. Thereafter, the temperature is raised very rapidly to volatilize the metal of interest. This technique has very good sensitivity and can be used to look at very low levels of analyte similar to those achieved by ICP–AES, but is prone to chemical interferences affecting the results. Also the analysis is slow and can be costly.

The demise of Chapter <231> means that modern techniques referred to above, and others, will now come become more common, and the old wet chemistry results will cease to be valid.

Conclusion

One can only sympathize with the scientists at USP that have responsibility for the standard pharmacopoeial methods involving heavy metals. Of the 4000-plus monographs in the *USP–NF*, there are approximately 1000 that specify a limit of heavy metals, in either a drug substance, excipient, or drug product (4). December 2012 marks the beginning of the end for Chapter <231> and the introduction of Chapters <232> and <233>. By May 2014, <231> will cease to exist, and by this point, validated procedures need to be in place to cover the removal of Chapter <231>. The 18 months between these dates may seem like a long time, but considering the number of existing monographs that contain the limit of heavy metals test, this timeframe seems very short. Overall, the *USP* changes, although daunting, can lead to improvements for the industry, including by better protecting the public through effectively tested medicines. Manufacturers will have peace of mind that they are providing clean and safe products to the market.

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PATH TO ZERO LANDFILL:
Learn How One Company is Leading the Way

LIVE WEBCAST: Tuesday, August 21, 2012, 11:00 am EDT

Register free at www.pharmtech.com/landfill

EVENT OVERVIEW:

This event will address the partnership between KIMBERLY-CLARK PROFESSIONAL, Life Technologies Corporation and Terracycle and how they have worked together to create a successful recycling program in cleanrooms and laboratories. Since the program's launch last Fall, Life Technologies Corporation is on pace to recycle over 5 tons of garments and gloves into plastic products such as park benches and picnic tables.

Learn how these global companies created a recycling platform and are making great strides in their path to zero landfill.

Key Learning Objectives:

- Learn how to improve your profile in sustainability indexes
- Find out how you can have an exceptional workplace that is safe, clean and sustainable
- Understand the sustainability advantages of using KIMBERLY-CLARK PROFESSIONAL* garment and gloves

Who Should Attend:

- Cleanroom Specialists
- Laboratory Professionals
- Lab Researchers
- Production Professionals
- Sustainability Professionals
- Quality Professionals
- CEO
- Environmental Health and Safety Professionals

PRESENTER

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Pharmaceutical-Based Cargo Security and Theft Prevention

Brad Elrod

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A rise in the incidence of cargo thefts in the pharmaceutical industry requires a cross-functional response from indvidual companies, the industry, law-enforcement organizations, and other stakeholders. The author discusses strategies for an proactive cargo security and antitheft program, including best practices used by Pfizer.

Brad Elrod is director of global conveyance security for Pfizer Global Logistics Compliance at Pfizer.

Cargo theft, for many years, was a problem that largely plagued the electronics industry, but criminals have recently shifted more attention to the far more lucrative pharmaceutical trade. In March 2010, thieves masterminded a heist of $75 million worth of cancer, psychiatric and blood-thinning drugs from a Connecticut warehouse by cutting a hole in the ceiling and dismantling alarms during a severe storm that masked their activities from the local authorities (1). To curb future cargo theft, it is imperative that pharmaceutical companies develop solid, globally applicable conveyance security programs.

A clear and present danger

The Connecticut incident drew a lot of attention to the level of sophistication used by organized crime when targeting pharmaceutical cargo. Soon afterwards, FDA issued a letter expressing its concern over the growing frequency of cargo and warehouse theft, the threat these activities pose to patient safety, and the need for manufacturers and others in the supply chain to take proactive, preventative measures (2). More important than the loss of property, when criminals reintroduce to the supply chain stolen medication that was not stored, refrigerated, or distributed as required to maintain product quality, unknowing consumers can receive tainted or ineffective drugs that could hurt or even kill them.

The rise in cargo theft is largely being fueled by the fact that penalties for stealing and distributing stolen pharmaceuticals are far less than dealing in illicit drugs, and the value of a single pharmaceutical shipment can be far greater than electronics, cigarettes, alcohol, or even firearms shipments. Surprisingly, in many cases, cargo theft is reported as "vehicular theft," a crime that carries a relatively low bond, which allows thieves to be quickly released to return to their work. Furthermore, a charge of vehicular theft also does not take into account the full value of the cargo. A top-of-the-line refrigerated truck costs about $500,000, but a pharmaceutical shipment could easily contain $20 million of product. The truck is most often recovered, but empty of its cargo.

Until criminal penalties are increased to reflect the cargo's real value and the potential risk to public safety, it is unlikely that this growing illegal activity will subside any time soon. Attention is growing in this area, with the FDA's Office of

Drug Security, Integrity and Recalls (ODSIR) targeted to specifically deal with counterfeiting, cargo thefts, and supply-chain threats in 2012 and legislation proposals such as the *Safe Doses Act*. For example, amendments introduced to the *Safe Doses Act* in May 2011 specifically addressed penalties, proposing increases of up to 20 years for pharmaceutical thefts.

Developing a cargo security and antitheft program

To develop a proactive cargo security and antitheft program, the first step is to understand how criminals work today, so newly installed systems are not protecting against yesterday's threat. Criminals are not restricted by corporate or governmental processes and are quick to adapt to changing preventative strategies. Recent trends observed in Brazil, for example, include the use of fake police checkpoints to intercept shipments (3).

The factors for cargo in transit vary, depending on the location around the world. Most cargo-jackings in the United State are nonviolent in nature and often occur when the driver goes into a rest stop and returns to find the truck gone. In other parts of the world, such as Latin America, cargo theft is more prevalent and can be more violent. Drivers are often kidnapped at gunpoint and later dumped in an isolated place. To complicate the situation, local police are sometimes complicit in the crime. Such conditions require out-of-the-box but potentially simple solutions. For example, to protect its employees and products, Pfizer sends only smaller shipments into these high-risk regions to make each cargo shipment less valuable and less desirable to potential thieves.

Freightwatch provides a succinct summary to the state of cargo theft globally in its 2011 report. "The volume of cargo theft grew throughout the Western hemisphere, with the United States, Mexico, Brazil, and other South American countries reporting substantial increases in theft," said the report. "By contrast in Europe, overall reporting of cargo theft rates were down while the average value per loss rose sharply, most notably in the United Kingdom, France and Germany" (4).

Despite appearances, these are not crimes of opportunity. Organized crime rings stake out facilities over time to gather information about the types and timings of shipments. Unfortunately, large-scale distributions systems cannot easily avoid routine schedules. There are other means of protecting cargo, however, some of them as simple as backing up a truck closer to the loading deck so those surveying the site cannot see what is being loaded and patrolling property perimeters to discourage unwanted observers.

Prescription medications are not the only target. Over-the-counter drugs and baby formula are at risk as well because they are relatively easy to resell. In general, most consumers do not think twice about buying a brand-name product at a flea market as long as the seal is intact. Few people stop to think about why the price is so low or consider that the product was probably stolen. If they did, they might also realize that the product was probably not handled in a manner designed to preserve quality or ingredient integrity.

Systems, relationships, and improved awareness

Cargo theft is committed by criminals that also poison the supply chain with counterfeiting, diversion, and economically motivated adulteration. Pfizer addresses these threats holistically through a comprehensive supply-chain security program. Conveyance security is one of the key pillars of the overall program. When a logistics or transportation system is strengthened against cargo theft, the touchpoints across quality, security, procurement, and other functions also are strengthened. Cross-functional systems linkages will prevent and detect more than one system alone.

As with most security systems, layered defenses are required to prevent cargo theft, and no single device or approach can be effective against all potential threats. Each situation is unique, and the level of security should result from a comprehensive risk assessment of all factors involved. Lower risk solutions include options, such as panic buttons, specially designed trailer and truck locks, satellite tracking, documentation controls, and background investigations and probationary periods for drivers. As the level of risk exposure increases, other techniques, such as door alarms, remote temperature monitoring, roof markings on trucks that can be identified from the air, and using two drivers, can be added to (not used in lieu of) the lower-risk prevention methods.

Focusing effectively on cargo theft requires a detailed and organized set of protocols. For example, Pfizer created and implemented global, regional. and site conveyance security policies and standards called Conveyance Product Care Requirements (CPCR) to ensure the safe and secure transport of its products. These requirements are clear and concise and acknowledge that transporting pharmaceutical products and materials throughout the manufacturing, packaging, storage, and distribution processes from raw-material acquisition through delivery to the customer is an integral aspect of supply-chain security.

Transporting processes must also be in compliance with all applicable regulations and be performed in a manner that ensures the safety, identity, strength, purity and quality of products during all transit activities. To this end, Pfizer has a designated Conveyance Security Council that oversees the following:

- CPCR management, implementation, and deployment
- Global tracking device application and deployment review
- Transportation risk analysis and threat matrix development
- Carrier-security rating processes and approvals
- Cargo-security protection methodology and decision matrix
- Incident tracking and reporting programs
- Seal use, application, and review
- Regional conveyance security variance reviews and approval.

Conveyance activities are coordinated externally and across any in-house function that touches cargo conveyance, including global security, import compliance, legal, quality, risk management, business continuity, and other

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Gauging Biopharm Outsourcing

Eric Langer

Budgets for biopharma activities are gaining in select functional areas, except outsourcing.

Planning and decision-making for the manufacture of biopharmaceuticals are becoming more complex as companies continue to implement cost-saving efforts, including outsourcing many support and even critical tasks. Companies must make difficult strategic decisions about commercial manufacture earlier in product development. A recent BioPlan Associates analysis found that essentially all biopharmaceutical developers use outsourcing services of some kind for the manufacture of clinical or commercial supplies, process development, R&D, assay services, fill–finish, or other activities (1).

Cost-cutting not a factor

The BioPlan survey, which included responses from 302 representatives from biopharmaceutical companies and CMOs in 29 countries, evaluated 23 key outsourcing areas in biomanufacturing (1). The study showed that companies are incorporating outsourcing as a manufacturing strategy rather than as an ad hoc method of adding flexible capacity or to simply eliminate overhead costs associated with lower value production activities. Data also show a spike in the percentage of biopharmaceutical companies projecting outsourcing of analytical testing, validation services, and fill–finish activities.

The BioPlan study further evaluated how companies are addressing cost issues in biopharmaceutical manufacturing. The survey identified activities biomanufacturers undertake to reduce costs. The study showed that outsourcing activities ranked in the bottom quarter of measured factors to reduce costs although outsourcing increased slightly for certain functions as a strategy for cost-containment during the past 12 months (see **Figure 1**). There was an increase in respondents using outsourcing of jobs in manufacturing to cut costs: 14.5% in 2012, up from 11.8% in 2011. Approximately 13% of respondents outsourced jobs in process development and 8.8% did in R&D. An equal number of respondents (9.4%) reported outsourcing manufacturing activities to domestic and nondomestic service providers. (see **Figure 1**).

Outsourcing budgets flat

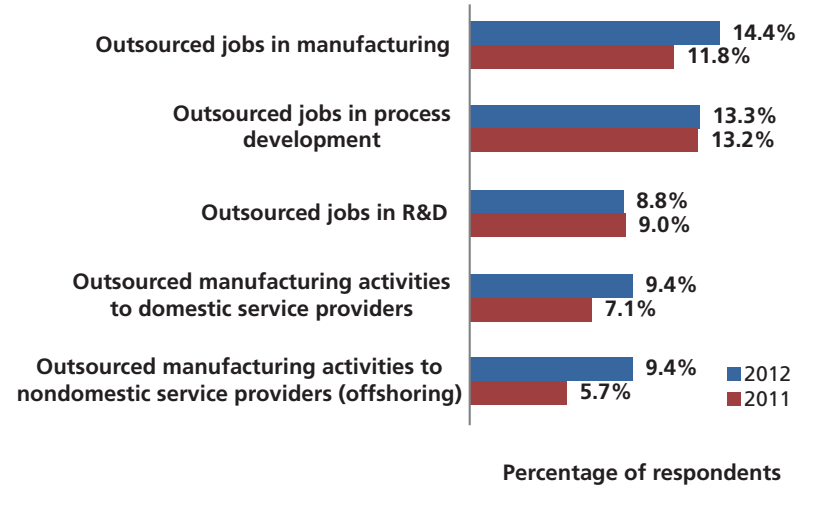
The survey showed clear evidence that budgets are bouncing back in all areas in 2012, except outsourced manufacturing. The uptick in areas other than outsourcing represents a change from two years ago when budgets decreased in areas ranging from production, hiring new scientific staff, and new facility construction.

The survey also separately asked respondents to indicate how their outsourcing in R&D and manufacturing will change during the next 12 months. On average, future outsourcing at individual facilities will see moderate overall increases for all types of outsourcing not just manufacturing (9.3% during the next 12 months). These increases are more heavily distributed on key outsourcing areas (see **Figure 2**) rather than broadly seen as increases across all operations.

Projections

The survey evaluated 24 different areas associated with outsourced operations and asked respondents which activities will be outsourced "more often" during the next

Figure 1: Outsourcing actions taken by biomanufacturers to reduce costs at facilities during the past 12 months.



Source: BioPlan Associates (1).

ALL FIGURES ARE COURTESY OF THE AUTHOR

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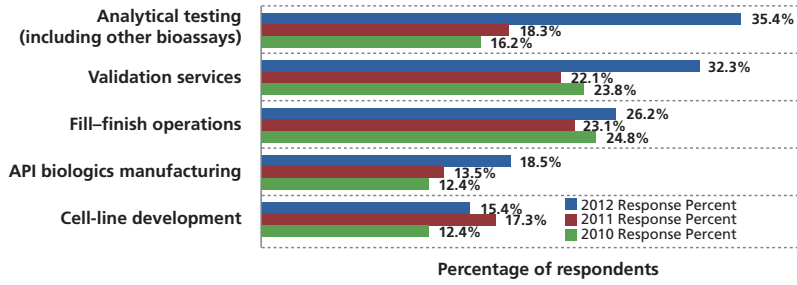
Figure 2: Select outsourcing activities projected to be done at significantly higher levels.



Source: BioPlan Associates (1).

24 months. More than one-third (35.4%) expect to increase outsourcing of analytical testing/bioassays. BioPlan believes much of this increase relates to product characterization, including for biosimilars.

Validation services was the area where respondents predicted the highest rate of increase (32.3% indicated high rates in outsourcing in 2012, compared with 22.1% in 2011 and 23.8% in 2010). Also, 26.2% of biomanufacturers predict they will outsource significantly more fill–finish operations during the next 24 months compared with 23% in 2011, and 25% in 2010. Other areas of outsourcing growth include: API biologics manufacturing,cell-line development, testing for lot release,and toxicity testing. Some recent decreases in predictions for outsourcing growth are in: downstream production operations, testing/product characterization, media optimization; upstream production operations, regulatory services, upstream process development; and testing cell-line stability.

Looking ahead

The biopharmaceutical industry continues to focus on productivity, efficiency, getting more out of existing internal resources, and maximizing performance from their provider relationships. Although outsourcing can improve overall efficiency and reduce costs, the management of relationships continues to be challenging and necessitates CMO/CRO flexibility to meet clients' shifting needs. Data from this study shows that CMOs are expanding their manufacturing competence through the use of novel technologies, single-use/disposable bioreactors, and other differentiated bioprocessing services. Improved services are resulting in increased adaptability, lower costs, faster turnaround, and higher yields, thereby offering more choice for biopharmaceutical companies. At the same time, the costs for using CMOs for product manufacturing are becoming slightly more competitive.

Reference

1. BioPlan Associates, *9th Annual Report and Survey of Biopharmaceutical Manufacturers* (Rockville, MD, April 2012), www.bioplanassociates.com. **PT**

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contin. from page 67

key functions. In addition to the CPCR, Pfizer functions work together to tighten security for warehouse standards and ensure the safe distribution of products to consumers in the marketplace. These processes are designed to protect the integrity of the legitimate supply chain against counterfeit goods getting in and to prevent legitimate product from being diverted or stolen.

Site and conveyance security also requires that companies develop close relationships with governmental agencies sponsoring supply chain security programs, such as the Customs-Trade Partnership Against Terrorism (C-TPAT) and Transportation Security Administration (TSA), to ensure compliance with regulations and to leverage current thinking and guidelines.

In addition, industry organizations such as the Technology Asset Protection Association (TAPA), the Pharmaceutical Cargo Security Coalition (PCSC), and Rx-360, the international supply-chain consortium, are important sources of practical information and best practices. At the local level, intelligence networks and a regional knowledge base need to be nurtured so reliable information can be shared with logistics managers, allowing them to better plan and improve transit and logistics operations.

Regardless of where in the supply chain a theft occurs, it is ultimately the manufacturer's responsibility–if not legally, then certainly in the equally important arenas of ethics and public opinion–for assuring that all parties fulfill their duties for delivering safe and effective medicines to customers.

A large part of the solution lies in raising awareness of the problem and currently available solutions. Much has already been published and discussed about counterfeiting, but little has been said publicly about cargo theft. Criminals tend to aim for the weakest link in a supply chain; once a crime such as cargo theft has been committed, the security system has already gone wrong. In today's environment, the pharmaceutical industry cannot afford to be complacent. Manufacturers need to stay one step ahead of organized crime by developing and coordinating top-notch conveyance and logistical security practices throughout their organizations to assure product and patient safety worldwide.

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2. FDA, "FDA Urges Industry to Take Additional Steps to Prevent Cargo Theft" Press Release (Rockville, MD, Apr. 28, 2010), www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm209911.htm, accessed July 18, 2012.
3. P. Taylor, "Brazilian Thieves Make off with 760 KShipment," *Securing Pharma.com*, Mar. 2, 2012.
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FDA Approves Generic Antitussive/ Antihistamine Product Developed by Three-Party Collaboration

Cornerstone Therapeutics, a specialty pharmaceutical company focused on acquiring, developing, and commercializing proprietary products, has announced FDA's approval of its abbreviated new drug application for CRTX 067, a generic hydrocodone polistirex and chlorpheniramine polistirex extended-release suspension.

CRTX 067 was developed through a collaboration including Cornerstone Therapeutics, Coating Place, and Neos Therapeutics. Cornerstone will market the product through its wholly owned generic-drug subsidiary, Aristos Pharmaceuticals. Coating Place will manufacture and supply the APIs, including a patent-protected version of time released hydrocodone and chlorpheniramine polistirex drug resin complex. The active substances will be manufactured at commercial scale in Coating Place's facilities. Neos developed the CRTX 067 drug-product formulation using its proprietary suspension formulation technology, Dynamic Time Release Suspension.

BMS Begins Tender Offer to Acquire Amylin

Bristol-Myers Squibb (BMS) has begun a cash tender offer to purchase all outstanding shares of common stock of Amylin Pharmaceuticals. Upon the successful closing of the tender offer, stockholders of Amylin will receive $31.00 in cash for each share of Amylin common stock validly tendered and not validly withdrawn in the offer, without interest and less any applicable withholding taxes. Following the purchase of shares in the tender offer, Amylin will become a subsidiary of BMS. BMS had previously announced its intention to acquire Amylin on June 29, 2012.

Seven Pharmaceutical Companies Join Academic Researchers for TB Drug Discovery

Seven pharmaceutical companies (Abbott, AstraZeneca, Bayer, Eli Lilly, GlaxoSmithKline, Merck & Co., and Sanofi) and four research institutions (the Infectious Disease Research Institute; the National Institute of Allergy and Infectious Diseases, part of the National Institutes of Health; Texas A&M University; and Weill Cornell Medical College), working with the Bill & Melinda Gates Foundation, have launched a partnership that aims to expedite the discovery of new treatments for tuberculosis (TB). The partnership, known as the TB Drug Accelerator (TBDA), will target the discovery of new TB drugs by collaborating on early-stage research. The goal of TBDA is to create a TB drug regimen that cures patients in only one month. Existing drugs, all at least 50 years old, require six months to cure the disease—a lengthy process that contributes to 20–30% of patients dropping out before completion. Aided by nearly $20 million from the Gates Foundation, the partners launched the TBDA in April 2012, and have begun the first round of screening for new TB drug candidates. The TBDA aims to develop five new preclinical drug candidates with treatment-shortening potential within five years and proof-of-concept for a one-month, three-drug regimen within 10 years.

Q&A with

Babu Padmanabhan, *Managing Director and Chief Knowledge Officer of STEER Engineering*

PharmTech:
How has the increasing focus on biopharmaceuticals affected your business?

Padmanabhan:
Our organization supports the bio/pharmaceutical industry by improving the effectiveness of the oral, skin, and intramuscular drug-delivery systems. We build the tools for engineering sustained and controlled release of drugs, enhanced bioavailability, drug-eluting stents, and implant-based, innovative drug-release systems. These methods are recent developments and have potential in both small-molecule drugs and biopharmaceuticals.

PharmTech:
How is your company responding to regulators' intensifying emphasis on inspections and product quality?

Padmanabhan:
Because we build tools for developing and manufacturing drug products, our equipment is built with full range of instrumentation and analytical systems that are compliant with current global regulatory requirements. We provide support in meeting the requirements of the design-, installation-, operational-, and performance-qualification protocols of various companies. Because of our exposure to many such protocols, our support to companies move them towards a better set of requirements (i.e., exceeding current requirements and preparing for the future).

PharmTech:
Do you see a new industry trend emerging?

Padmanabhan:
Continuous manufacturing is gaining significant attention among the pharmaceutical industry. Life-cycle management of existing drugs has been one of the current areas of focus. There is growing interest in equipment that supports the manufacturing of potent compounds with containment.

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Are you ready to meet the global pharma industry?

CPhI Worldwide, the leading pharmaceutical exhibition, is returning once again, offering pharma executives an opportunity to source new suppliers, network and learn more about the industry. CPhI Worldwide is being held at Feria de Madrid, Spain, from 9–11 October 2012. The show is an opportunity for pharma executives to find new suppliers, build their professional networks and learn more about the key trends in pharma today.

CPhI Worldwide has a genuinely global focus, attracting visitors and exhibitors from all over the world with everything available under one roof. Last year's event, held in Frankfurt, attracted over 2,200 exhibitors from over 140 countries and more than 30,000 attendees.

Entire pharma value chain under one roof

CPhI Worldwide actually comprises four co-located shows. In addition to CPhI, which focuses on Pharma Ingredients, there is ICSE for Pharma Contract Services, P–MEC Europe for Pharma Technology, Equipment and Machinery and InnoPack for Pharma Packaging.

Together, the shows cover every stage of the pharma value chain and cater to the specific needs of a diverse range of pharma stakeholders, with exhibitors in every area from ingredients, excipients and formulation through to finished dosage, technology and packaging.

CPhI's unique structure has been developed to reflect the interdisciplinary synergy that characterizes pharma today. For example, bringing a successful OTC medicine to market means getting every element just right: not just the formulation, but also the manufacturing process, the packaging or delivery system and the contributions made by contracted service providers.

The structure also allows visitors to shape their own experience of the event, focusing on the suppliers and technologies that interest them most while also exploring related areas of the industry.

New zones and global pavilions for 2012

All four shows within CPhI are subdivided into zones, each dedicated to a different area of expertise within the sector and designed to showcase its distinct qualities. Zoning has been warmly received by attendees because it makes the event easier to navigate and enables quicker movement between areas.

This year, the event features two specialized areas devoted to biopharmaceutical development resources: the Biopharmaceuticals and Bio Services Zones.

The Biopharmaceuticals Zone focuses on biopharmaceutical ingredients and products such as Bio Clusters, Biopharmaceuticals, Bio-similars, Bio process technologies, Biotechnology and related specialities, Platform Technologies and Therapeutics.

The Bio Services Zone is devoted to companies offering bio services and technology to the pharma industry.

Other zones at the show focus on a diverse range of specialist disciplines and product areas. CPhI features zones for APIs, Generic APIs, Custom Manufacturing, Fine Chemicals, Intermediates, Finished Dosage, Excipients/Formulation, a General zone and the new Biopharmaceuticals zone. ICSE includes the Bio Services zone, plus zones devoted to Logistics and Supply Chain, Analytical and Lab Services, Clinical Trials (including Pre-Clinical Trials, Clinical Trials Stages 1–4, CRO and Clinical Data Management), and a General Floor.

P–MEC Europe features LABWorld, which focuses on laboratory, analytical and biotechnology instrumentation. Finally, InnoPack's two zones are dedicated to Labeling and Track & Trace.

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CPhI is a truly global event, attracting exhibitors and visitors from around the world. Recognising that some visitors have an interest in a particular geographical area as well as a particular sector, the event includes 16 Global Pavilions that allow people to find suppliers from a specific region quickly and easily. This year, new Global Pavilions have been added for Russia and Malaysia, reflecting the rapid growth of the pharmaceutical industry in these markets. The other Pavilions focus on Argentina, Brazil, China, Egypt, France, India, Ireland, Korea, Morocco, Portugal, Scotland, the UK and North America, which now features SOCMA.

The choice of the senior executive

CPhI is renowned within the pharma industry for the audience it attracts, even in comparison to other pharma-specific events. Many C-level executives attend the show; in 2011, 6 out of 10 visitors had sole or joint purchasing responsibility for the types of products and services at the show, and 80% of visitors planned to purchase products or services from an exhibiting company. Because of this strong commercial focus, the event attracts many exhibitors who return year after year; many have put CPhI Worldwide at the heart of their new-business efforts.

Time and again, exhibitors report that having a stand at CPhI Worldwide puts them in front of senior commercial decision-makers, allowing them to forge highly productive, long-lasting business relationships face to face. Many find that their attendance unlocks new business opportunities that would have been difficult or impossible to realise through other marketing channels.

Together, the shows cover every stage of the pharma value chain and cater to the specific needs of a diverse range of pharma stakeholders.

In 2011, 94% of visitors were somewhat to very satisfied with their experience of the show, and 83% agreed that CPhI is a "must attend" event.

Rewarding achievement

For the last few years, CPhI has hosted the Innovation Awards, which recognize outstanding innovation among the event's exhibitors. This year, the scope of the awards has been broadened, and they've been renamed accordingly, becoming the CPhI Pharma Awards.

The awards aim to honour companies who turn inspiration into innovation—the thinkers and creators breaking new ground in manufacturing, drug delivery, sustainable packaging and stand design. Success in the awards delivers exposure on the international stage, as award winners are unveiled to the global trade press during the event. Naturally, winners take advantage of a major commercial op-

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portunity, as their newly developed products and services are directly promoted to the many 'movers and shakers' present at the show.

The CPhI Pharma Awards feature three categories: Best Innovation, Best Sustainable Packaging and Best Sustainable Stand Design. Best Innovation recognizes outstanding achievement in pharmaceutical R&D, highlighting pioneers in new, commercially scalable technologies.

Best Sustainable Packaging, newly introduced for 2012, rewards Pharma packaging companies who have created a specific material, machine or service that allows pharma companies to achieve a more sustainable packaging, or packaging process. The creation of this award reflects the industry-wide move towards more sustainable materials and processes.

The Best Sustainable Stand Design award celebrates exhibitors who have taken positive steps towards sustainability in the design and construction of their stands—using green materials, reusing, recycling and so on.

The Best Sustainable Stand Design award is just one of a range of sustainability initiatives being undertaken by UBM Live, the organizers of CPhI Worldwide. UBM Live was the first major event organizer to achieve self-certification under BS 8901, with the Amsterdam office being accredited in November 2011. Soon afterwards, the standard was rolled out to events organized by UBM Live. Now the company is working towards ISO certification, which will take its commitment to sustainability to the next level. A dedicated Sustainable Feature area will also be available at CPhI.

Entry for the CPhI Pharma Awards is open to exhibitors at CPhI Worldwide, ICSE, P-MEC Europe and InnoPack. The deadline for Best Innovation and Best Sustainable Packaging is 10 August 2012, while Sustainable Stand Design is open until 31 August. The shortlist will be announced on 7 September, with presentations being held by shortlisted exhibitors at the CPhI Speakers Corner on 9 October. Details of how to enter can be found online at **www.cphi.com/pharma-awards**.

CPhI Global Meetings

The commercial opportunities available at CPhI are significant: the average visitor holds a departmental budget of over €3.7m and makes eight new business contacts while at the show. With so many potentially relevant stands and just three days to see them all, there's always a risk that exhibitors and visitors will fail to connect with their ideal commercial partner.

The average visitor holds a departmental budget of over €3.7m and makes eight new business contacts while at the show.

Anxious to avoid this, many attendees have taken to pre-arranging their meetings with exhibitors; the average visitor attends 16 meetings at the show, of which nine are pre-arranged. The success of this depends on visitors carrying out proactive research in order to identify who they should see. This year, for the first time, the event's

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organizers are offering an official 'Match and Meet' service—a sort of matchmaking service for attendees.

CPhI Global Meetings give exhibitors direct access to senior-level executives such as procurement managers, contract managers and business development managers from across the entire pharma industry. It allows them to meet pre-qualified buyers who are actively looking for new partnerships, products and services.

The service is fully tailored around the needs of exhibitors and visitors, who can simply request meetings based on their areas of specialization. They are then carefully matched up with hand-picked buyers, using the buyers' purchasing requirements as a guide. One week before the event, a list of matched meetings is submitted for the exhibitor's approval.

The system typically delivers four or five meetings per supplier, each scheduled to last around 20 minutes and held at the exhibitor's own stand or in a dedicated meeting area.

Conferences and seminars

Another reason to attend CPhI Worldwide is the impressive array of conferences, talks and seminars, which allow visitors and exhibitors to develop their industry knowledge and keep up to speed with emerging trends.

The Pre-Connect Conference will be held on October 8, the day before the main event opens for business. Visitors willing to invest an extra day can take advantage of a programme split into two halves on Development and partnering and Manufacturing—or mix and match modules between the programmes.

Development and partnering features modules on Generics and super-generics, Biosimilars and biobetters and Strategic partnerships, while Manufacturing covers Drug delivery systems, API sourcing in emerging markets and Biomanufacturing. Both programmes run from 8:30 am to 8 pm, including breaks for networking and tapas and an evening drinks reception.

Once CPhI Worldwide opens the following day, attendees can take advantage of a wide range of lunchtime education sessions, each focusing on a key topic in pharma today. The full programme has yet to be confirmed, but based on previous years the sessions are sure to be relevant, authoritative and hugely popular with visitors.

For those with less time to spare who want to get up to speed with some recently launched innovations, the Speaker's Corner areas provide the facility for exhibitors to deliver 20-minute 'bite-sized' speeches on their new launches. Speaker's Corners are situated in CPhI, ICSE and InnoPack.

Enjoying Madrid

When not at the event itself, attendees can enjoy the many attractions of Madrid, from the Puerta del Sol, Royal Palace and Almudena Cathedral to the world-famous Prado Museum. Visitors can also enjoy the city's famous nightlife, café culture and shopping opportunities.

More information

- A custom-built Mobile App is in development that will offer quick, easy access to key information about the CPhI event. More details will be published at the CPhI website (**www.cphi.com**) and via the event's social media channels.
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- **Parenteral Delivery Systems**
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Bilcare Research employs more than 2,000 people and has a global footprint with modern manufacturing and R&D plants across the United States, Europe, India and Singapore. Its U.S. headquarters is located in Delaware City, DE, and offers 180,000 square feet of space, including the new BilcareOptima™ R&D lab.

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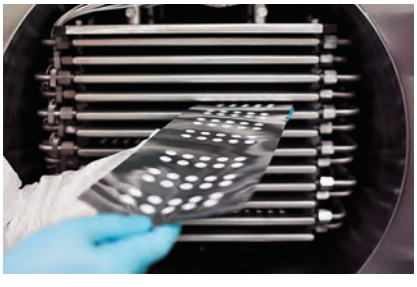

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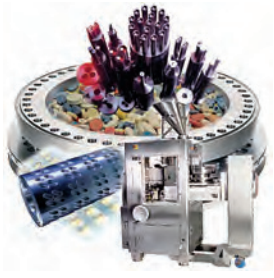
Save time, improve efficiency, and streamline cleaning with the PharMix SC System. From complex to simple, we'll design a system for your specific application. The SC System improves costs by reducing the need for capital equipment and also reduces your costs on labor, validation, manufacturing, and utilities; virtually eliminates equipment cleaning.

The Elizabeth Companies

601 Linden St.
McKeesport, PA 15132
tel. 412.751.3000
fax 412.751.2390
www.eliz.com



Total tableting solutions

The Elizabeth Companies, a leading manufacturer of tooling, presses, and parts for the pharmaceutical industry, is a source for total tableting solutions. From tablet tooling, presses, and parts to blisterpackaging tooling, the company offers high-quality products combined with a strong commitment to service. With more than 50 years of tableting expertise, the company is committed to helping customers meet their tableting needs.

Tablet tooling

When making tablet tooling, the Elizabeth Companies starts with high-quality tool steel, carbide, and ceramic, then incorporates skilled tool- and tablet-design engineering, the latest in computerized machine tools, expert craftsmanship, and scrupulous quality control.

Press replacement parts and rebuild services

Tableting-press replacement parts and press refurbishing services are offered through Elizabeth Scheu & Kniss, a supplier of tablet-press turrets and parts. A line of high-quality turrets and a wide variety of replacement parts for various makes and models of presses are in stock and ready to ship.

Interchangeable turret tablet press

The press's removable turret and "Easy Clean" design facilitate part removal and changeover between product runs. Its interior is easily accessed, and there is less weight on heavier press components. Single-sided models are designed to achieve turret speeds of 100 rpm, and double-sided models also are available for high-volume production.

Eliza-Press

Elizabeth is offering a new line of tablet presses, the Eliza-Press Series. The Eliza-Press 200 model is the new R&D size with both single and bi-layer versions. This new series is designed as a semi-automatic tablet press engineered with quality, performance, and value. Fully GMP compliant with a simple user-friendly touchscreen interface.

Hata 3-Layer/Core Press

The New Hata 3-Layer Tableting Press System with an interchangeable turret design has the production capabilities of single-layer, bi-layer, tri-layer, and a custom core-tableting application. All of this production flexibility in one Hata Tableting Press. Mechanical design features on the Hata Press aid in consistent weight control of the individual tablet layers. Along with Hata's patented sealed feeding system, a special vacuum design also assists with the reduction of cross-contamination for accurate multi-layer production.

EtQ, Inc.

399 Conklin St.
Farmingdale, NY 11735
tel. 516.293.0949
www.etq.com
info@etq.com

EtQ for Pharmaceuticals

EtQ is an integrated Quality and Compliance Management system that has been pre-configured to specifically address the needs of the Pharmaceutical industry. EtQ's unique modular approach provides unparalleled flexibility and automation, delivering a best in class solution. Key modules include Change Management, Complaint Handling, Risk Management, and Audits.

Change Management

EtQ's Change Management module is designed to manage all aspects of the Change Management process. Change Management integrates with other key modules such as Risk Register to analyze the impact of change, and Complaints Handling to identify adverse events, analyze change feedback, and collect customer requirements for future changes.

EtQ's Electronic Signature and Record

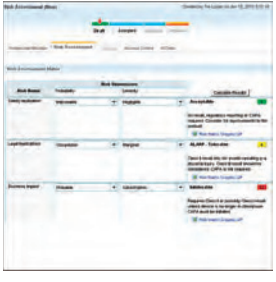
EtQ's FDA Compliance Management Software automatically and securely binds the authenticated user's electronic signature. EtQ ensures that the user has signed onto the system and exposed their signature via the forced authentication process, as required by 21 CFR Part 11. Authentication is required each time a document is processed.

Complaint Handling

Complaint Handling Management Software manages complaint handling in compliance with FDA guidelines. It records all complaints reported by customers or consumers to investigate the problems and keeps records of these complaints. Complaint Handling Software also provides an eMDR form, for adverse event reporting.

EtQ eValidator

For companies regulated by the FDA, systems validation is a necessary requirement to ensure a secure environment. EtQ's eValidator utility is designed to automate the PQ process. Using the eValidator to run validation scripts can automate the validation process by as much as 400%.



EtQ Risk Register

EtQ's Risk Register tool calculates risk using a variety of techniques, updates risk at multiple points in the process, and displays risk mitigation history by event. Users can identify risk scores and related actions, view risk charts, build risk histories, and use configurable views to determine top risks in the quality system.

Fette Compacting America

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sales@fetteamerica.com

Fette Compacting America Introduces FE35 Tablet Press, Offering Fastest Changeover Time in Class

Fette Compacting America, the leading supplier of tablet press equipment for pharmaceutical and nutritional applications, now offers the FE35 Tablet Press, whose attributes include unprecedented levels of productivity and the fastest changeover time in its class. The new machine offers unmatched flexibility and equipment availability – important considering the pharma industry's rapid growth in new markets, shorter product lifetimes and rising cost pressures.

The FE35 is a single rotary tablet press that can be fitted with up to 51 stations to produce up to 367,000 tablets per hour. The machine is clad in easily-detachable, FDA-certified high-performance polymer panels and offers 360-degree access, and its geometrically optimized surfaces offer easiest-possible handling and fast cleaning. Other highlights:

- Innovative filling system for easy, reliable feeding and increased product output
- New rotor design for maximum yields, minimum product loss and easy changeover
- New compression stations for fast format and product changeover
- Novel internal tablet discharge for guaranteed uninterrupted production
- New flexible vacuum cleaning system for short cleaning cycles
- Turret removal in 15 minutes involving only 10 components and zero tools

New Compression Stations

For shorter refitting time, the FE35 is the only machine in its class with upper and lower compression rollers that can be adjusted automatically, as well as pressure measurement cells with integrated measuring amplifiers and drive units with a new position measurement system.

New Drive, Turret and Discharge

The FE35's direct torque drive offers energy-efficient, zero-maintenance operation. For maximum flexibility, a switch cabinet can be positioned externally or internally, and the machine's power cabinet features an innovative cooling design. Turret changeover set-up includes cams and punches and is segmented to permit expedient refitting. Other turret features include a coded tablet scraper and coded filling cam detection, as well as a central, multi-function connector for oil, air and electricity.

Ease of Operation

- Unprecedented ease of operation, changeover and maintenance
- Fette's Human Machine Interface (HMI) offers uncomplicated, intuitive operation for maximum efficiency and security. Highlights:
  - Key electronic data, including CPU, I/O and amplifier status, can be monitored on the HMI in real time
  - An SQL server database
  - Swift access to the machine's most important functions via 12 pictogram buttons

GEMÜ Valves

3800 Camp Creek Parkway
Bldg. 2600, Suite 120
Atlanta, Georgia 30331
tel. 678.553.3400, fax 678.553.3459
www.gemu.com

The Gemu 651 unitized valve / actuator / pilot valve / position indicator, offers a unique solution in confined areas, particularly for fractional sized valves and small multiport configurations. The control top segment is interchangeable with a 4-20 electro-pneumatic positioner module.

The Gemu 1236 Position Indicator features highly visible luminous indication, self setting switch points and local or remote programming. Continuous analogue sensing with microprocessor controlled setting offers enhanced repeatability and reliability. Optional AS-I interface or IO-LINK enabled communication.

The Gemu 1434 Electro-pneumatic Valve Positioner is smart but not superfluous. It offers a plug and play, auto-initializing positioner for linear valves up to 25 mm stroke in a stainless steel economical NEMA 4X enclosure. Remote mounting is optional.

The NEW Gemu 4242 Combi Switchbox Innovative continuous sensing with microprocessor controlled set point determination offers unprecedented repeatability and reliability in valve position feedback. Features include highly visible GLOWTOP indicator, self setting without cover removal and local or remote programming. The integrated 3/2 pilot valve with manual override is included in a common stainless steel enclosure. Fieldbus options include AS-I and DeviceNet.

M600 Multiport Sanitary Block Valves provide solutions to piping challenges, retained volume limits, drainability issues and space constraints while providing enhanced efficiency and simplified validation. A broad range of porting configurations facilitates modeling in complex piping systems.

The Gemu 688 Sanitary Diaphragm Valve provides two-stage flow with an intermediate setting that is mechanically adjustable from 0 – 100%. Fast and precise filling rates with reduced foaming or frothing are attained in a single valve for dribble control without a costly modulating control system.

Hospira One 2 One®

275 North Field Dr.
Lake Forest, IL 60045
tel. 224.212.2267
tel. +44 (0) 1926 835 554
one2one@hospira.com
www.one2onecmo.com

ONE 2 ONE™

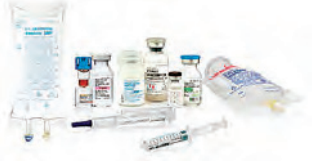
Parenteral Contract Manufacturing Service of Hospira

Hospira's One 2 One® business is a world leader in the custom development and manufacture of injectable products packaged in vials, prefilled syringes, cartridges, and ampoules. Hospira has over 80 years of know-how in parenteral drug commercialization, and One 2 One has over 20 years of contract manufacturing experience serving the bio/pharmaceutical companies.

By centralizing management, One 2 One can thoroughly integrate five state-of-the-art manufacturing facilities around the world. Our global network of facilities offers a wide range of development, drug delivery, and manufacturing capabilities and services. One 2 One has a wealth of history and experience in global injectable product commercialization.

Broad Sterile Manufacturing Experience

- Sterile filling and lyophilization in the U.S., Italy, Australia and India.
- Manufactured over 25 different monoclonal antibodies, proteins, peptides and recombinant vaccines.
- Extensive experience manufacturing emulsions, cytotoxic products and beta-lactam products.
- Practical knowledge of 70 markets, including expert regulatory filing strategies for the Americas, Europe, Asia Pacific regions.



Drug Delivery Systems

One 2 One provides a wide variety of delivery options, from vials, bottles, and prefilled syringes, to proprietary products such as the VisIV™ flexible container. It's about developing simple solutions to streamline administration, improve accuracy, and decrease waste and costs. One 2 One meets your unique product needs for a distinct advantage in the marketplace.

iSecure™ Prefilled Syringe

As a prefilled, unit-dose disposable injection syringe, iSecure™ delivers efficiency and simplicity to ensure accuracy and lower costs. iSecure™ utilizes a 1 to 2.5 mL cartridge and is designed for compatibility with intravenous administration sets and has the flexibility to be used for intramuscular injections.

Onco-Tain™ Vial

Our proprietary Onco-Tain™ vial packaging option was designed to contain cytotoxic material by providing shatter resistance with a PVC bottom, surface protection with a shrink-wrapped sleeve and clarity of glass for easy inspection. We highly recommend this vial packaging option for your cytotoxic products.

International Centre for Diffraction Data

12 Campus Boulevard
Newtown Square, PA 19073
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fax 610.325.9823
www.icdd.com

PDF-4/Organics

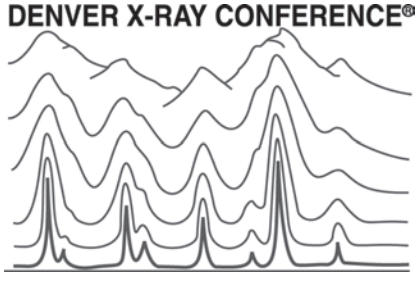
Our materials identification database provides comprehensive coverage as the world's largest X-ray powder diffraction database for organics and organometallics. PDF-4/Organics is designed for a multitude of applications in pharmaceutical, regulatory, specialty chemical, biomaterials, and forensic fields. PDF-4/Organics is produced by combining drug active compounds with polymers (including starches and celluloses), common inorganic salts, excipients, and pharmaceuticals.

PDF-4+

PDF-4+ is an advanced database designed for both phase identification and quantitative analysis. The comprehensive collection of inorganic materials, produced in a standardized format can be rapidly searched for unknown identification. It contains numerous features such as digitized patterns, molecular graphics, and atomic parameters. Many new features have been incorporated into PDF-4+ to enhance the ability to do quantitative analysis by any of three methods: Rietveld Analysis, Reference Intensity Ratio (RIR) method, or Total Pattern Analysis.

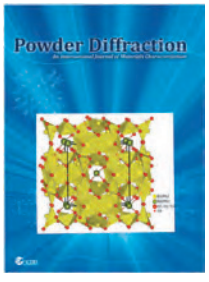
Pharmaceutical Powder X-ray Diffraction Symposium

This annual symposium is designed to create a forum for the exchange of knowledge and cutting-edge ideas among those interested in the combined fields of XRD and pharmaceutical sciences. PPXRD presents topics on patent and regulatory issues, formulation, product development, drug delivery, polymorphs, amorphous and nanomaterials, and complimentary techniques.



Denver X-ray Conference

DXC is the world's largest annual conference dedicated to the fields of X-ray analysis. Experts in the field of X-ray diffraction and X-ray fluorescence gather for a week of workshops, technical sessions, and manufacturers' exhibits. For information on the conference please visit www.dxcicdd.com.



Powder Diffraction Journal

ICDD's quarterly international journal focuses on materials characterization employing X-ray powder diffraction and related techniques. With feature articles covering a wide range of applications, from crystal-structure determination of polycrystalline materials to advances in application software and hardware, this journal offers a wide range of practical applications.

ICDD Clinics

ICDD offers a variety of educational products designated to teach both the new and experienced user. ICDD Clinics boast a high instructor to student ratio. Our group of experienced instructors with diverse scientific backgrounds enables the attendees to receive a blend of both theory and results-oriented practical experience. The week-long format provides in-depth training, not offered in most other workshops and symposia.

Lancaster Laboratories

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PO Box 12425
Lancaster, PA 17605-2425
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www.lancasterlabspharm.com

Biopharmaceutical Services

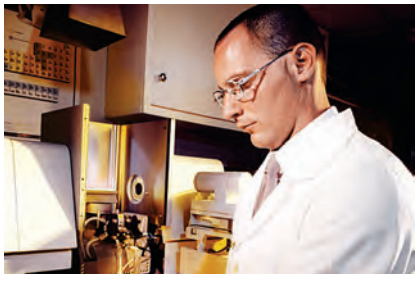
Lancaster Laboratories provides a broad range of laboratory services supporting the biopharmaceutical industry. These services include cell and molecular biology (cell-based assays, ELISA assays, nucleic-acid analysis, PCR, cell-line testing), virology (viral safety and viral clearance), biochemistry (biochromatography, electrophoresis, mass spectrometry, protein quantitation and characterization), and support for facility and process validation.

Method Development/Validation

Our staff of scientists offers extensive method development and validation services. Methods for stability and release testing, as well as, process and cleaning validation, in support of large and small molecules drug products, drug substances, comparator products, excipients and raw materials are offered. Method qualification/validation can be conducted using protocols developed by Lancaster Laboratories or the client.

Stability Services

We specialize in supporting stability studies, with services ranging from protocol writing to storage and testing through tracking and trending of data. The company is experienced in testing solid-dosage forms, liquids, suspensions, transdermals, aerosols, and comparator products. Stability storage consists of 26 different temperature and humidity conditions with more than 30,000 ft^3 of storage space.



Raw Materials Services

Lancaster Laboratories provides extensive capabilities in Raw Materials testing. Testing is conducted using compendia (USP, EP, JP, BP, FCC, ACS) and client/vendor supplied methodology. A multiple shift operation with extensive laboratory capacity provides exemplary service and meets delivery needs. Expedited and customized programs are also available upon request.

Microbiology

In a 9000-ft^2 suite of laboratories designed for efficiency and contamination control, Lancaster Laboratories performs a full array of microbiological testing in support of sterile and nonsterile products and environmental monitoring and control. Services include sterility testing using isolator-barrier technology, mycoplasma testing, endotoxin and preservative-effectiveness testing, microbial limits testing and organism identification, and laboratory support for facility validation.

Innovative Scientific Staffing Solutions

Our innovative Professional Scientific Staffing services solve pharmaceutical and biopharmaceutical clients' co-employment challenges. Professional Scientific Staffing provides our full-time scientists at the client's facilities; while Full Time Equivalent offers dedicated analysts for clients' projects at our facility. Award winning HR best practices, IRS 20-Factor indemnified and 50-year outstanding laboratory services reputation available at your site or ours.

Meissner Filtration Products

4181 Calle Tesoro
Camarillo, CA 93012
tel. 800.391.9458
+1.805.388.9911 (International)
www.meissner.com

UltraCap® H.D. Capsule Filters

High Capacity UltraCap® H.D. capsules provide single-use convenience for critical filtration applications requiring high-flow/throughput. UltraCap® H.D. is available in T-style and Inline versions, and can be selected in 10", 20", 30", 40" and 50" lengths. Robust in design, the UltraCap® H.D. performs well in demanding environments.

TepoFlex® & FluoroFlex® Biocontainers

Meissner drives innovation with industry firsts - TepoFlex® - the industry's first PE based biocontainer without slip agents - and FluoroFlex® - the industry's first multilayer PVDF biocontainer. TepoFlex® 2D & 3D biocontainer assemblies are available in standard configurations (50 mL – 1,000 L). FluoroFlex® is available in standard 2D configurations (50 mL – 20 L).

One-Touch® Single-Use Systems

Meissner's One-Touch® single-use systems portfolio optimizes fluid handling for the biopharmaceutical industry. Designed to offer unprecedented fluid integrity performance, TepoFlex® biocontainers can be deployed in FlexStation® rigid outer containers for shipping and storage needs, or in QuaDrum™ containers for intra-facility mobility and storage. Visit www.meissner.com/onetouch for more information.

BioFlex™ Tubing Assemblies

BioFlex™ tubing assemblies are designed for secure fluid transfer in critical biopharmaceutical processing applications. These single-use tubing and filter/tubing assemblies offer maximum convenience and flexibility in single-use systems. They can also be used in conventional or hybrid facilities to connect single-use and stainless steel processing equipment.

Membrane Filters

Membrane filters (0.04 µm - 1.0 µm absolute) are available in SteriLUX® and Steridyne® PVDF, EverLUX® and STyLUX® PES, Chemdyne® PP, and Ultradyne® PTFE. Configurations range from syringe and disc filters, to capsules and high capacity capsules and cartridge filters. (Microfiber prefilters to 99 µm are also available in PP, glass fiber and depth media.)

UltraSnap™ Filter Assembly

The UltraSnap™ filter assembly eliminates the time and expense associated with change-out of filters from stainless steel housings and associated cleaning/reassembly of the filter/housing unit(s). Time saved from cleaning operations results in less downtime between filtration runs, and improved productivity. Its very low hold-up volume minimizes product loss during change-outs and ensures maximum product recovery.

Metrics, Inc.

1240 Sugg Pkwy.
Greenville, NC 27834
tel. 252.752.3800
marketing@metricsinc.com
www.MetricsInc.com

Company Overview

Metrics Inc., a fast-growing CDMO, occupies a 92,000-ft^2 state-of-the-art analytical testing, pharmaceutical development and manufacturing facility. Our veteran formulation development staff averages more than 17 years' career experience in pharmaceutical development and is supported by a team of 130+ analytical chemists. Services include oral dose formulation development, analytical method development and validation, microbiological testing, stability storage and testing, raw material release, trace element testing, and routine analysis of dosage forms.

CTM Phase I, II, III

Metrics' expanded CTM capabilities offer greater capacity with all clinical trial phases. Our new flexible manufacturing facility and equipment can handle up to 450-kilo batch sizes. Metrics also offers expertise in over-encapsulation for comparator studies, as well as potent drug handling capabilities. CTM packaging and labeling is also available.

Commercial Manufacturing

Seven large-scale manufacturing and packaging rooms for Phase III clinical trial and commercial manufacturing ensure high-quality manufacturing of solid oral dose formulations, including DEA II-V controlled products. Full analytical support is available – release testing, stability, microbiology testing, and custom analytical development and validation.

Fast-Track First-Time-In-Man Studies

Metrics has successfully delivered material for more than 130 critical FTIM studies. Our process ensures speed and accuracy, with a 16-24 week timeline from receipt of well-characterized NCE to shipment. Services include handling of potent products, stability studies, analytical methods development and validation. Choose blended powder in capsule or pure API in a labeled bottle.

Potent Products

Metrics' segregated potent facility provides total engineered containment through customized, hard-wall isolation technologies. Containment is achieved at 30 nanograms pcm of room air; equipment and change parts are dedicated exclusively to potent use. The facility features independent entry, exit and equipment double airlocks, decontamination showers, dedicated washroom, dedicated equipment storage and pass thru for product/waste.

Pharmaceutical Formulation Development

Services include: Tableting, instant release, controlled/matrix release, bi-layer, sustained release, capsule filling, over-encapsulation, milling, micronizing, enteric coating and liquids. Metrics' processes included handling of potent products. Metrics' SOPs are geared toward all phases of the FDA submission process.

Mettler Toledo

1900 Polaris Pkwy.
Columbus OH 43240
tel. 800.638.8537
www.mt.com

pH

Mettler Toledo offers a wide range of quality pH meters and superior sensor technology, so whatever your measurement challenge, we have the tools to meet your needs. Our focus is on quality products with simple, intuitive operation. To learn more about our comprehensive product portfolio, visit us at www.mt.com/ph

Dropping Point

Dropping and softening point determination has never been so simple, secure or reproducible. The all-new, innovative METTLER TOLEDO dropping point systems provide automatic, objective and video-recorded analysis for unparalleled certainty of results. One Click™ shortcuts, standard-compliant methods and built-in user management ensure peace of mind. Visit www.mt.com/one-click-dropping for more information.

Melting Point

Melting Point Excellence delivers simultaneous, straightforward and automatic determination of melting point or range of up to six samples. Sophisticated, yet intuitive software simplifies statistical evaluations, provides user management and ensures compliance. Color video playback with 6X magnification allows investigation of unexpected results. Qualification support is available.
Learn more: www.mt.com/one-click-melting.

Density and Refractive Index

LiquiPhysics Excellence systems measure Density, Refractive Index and related values with precision and ease. Modularity provides the ultimate in flexibility by allowing standalone instruments to be upgraded by addition of modules to increase throughput through automation or enhance measuring parameters as your needs change. Go to www.mt.com/liquiphysics for more information.

General Titration

Titration Excellence line features One Click Titration™, a milestone in solutions for simple, efficient and secure titration. The modular Excellence line is tailored exactly to your needs and is intuitive and easy to understand. With improved efficiency through intelligence and automation, you have the control every successful company requires.
Learn more: www.mt.com/one-click-titration

Karl Fischer Titration

With the METTLER TOLEDO Karl Fischer titrators, your operators need to only press one button for accurate and precise results within minutes! Safety is no longer a concern with our Solvent Manager reagent handler, along with the security your expect from us with LabX® titration software. Learn more:
www.mt.com/one-click-titration

Natoli Engineering Company, Inc.

28 Research Park Circle
St. Charles, MO 63304
tel. 636.926.8900
fax 636.926.8910
www.natoli.com

Tablet Compression Tooling

For over 35 years, Natoli has provided their customers with the highest quality tooling in a variety of options, including carbide-tip, multiple-tip, micro-tab, rotating heads/tips, IMA Comprima, Kilian-type, 3-D exotics, die segments, and more. Natoli also offers a large selection of steel types and coatings to meet your specific needs.

Tablet Presses

Natoli offers a diverse line of tablet presses to meet specific tableting needs. The NP-RD10A single-station laboratory press is ideal for R&D when only small samples are available. The NP-500 series is a double-sided, rotary press designed to compress tablets requiring extra deep fill and extended dwell time.

Tablet Press Replacement Parts and Turrets

Natoli stocks over 300,000 quality replacement parts for nearly every tablet press on the market, making it possible to receive the part you need the very next day. Natoli also offers refurbishing services for a wide range of tablet presses.

Tool Inspection and Control System

The LVS inspection device features modern dual laser technology to ensure accurate measurements, which are automatically recorded in the powerful TM-II database. Designed to help tablet manufacturers improve tablet quality and consistency, the LVS/TM-II control system measures and organizes critical punch inspection dimensions through a user-friendly, comprehensive tooling database.

Tablet Compression Accessories Catalog

The newly redesigned catalog now features two additional sections – *Tablet Press Parts* and *Encapsulator Parts* – and dozens of innovative new products. Printed catalogs are available by request at no charge and the interactive digital version is now available on the Natoli website.

Technical Services

Natoli provides technical support, troubleshooting, training, and laboratory services to help customers overcome common tableting problems such as sticking and picking. Natoli experts evaluate tablet and tooling designs and experiment with dozens of combinations of steel types and coatings to determine the most efficient and effective solution to the customer's specific issues.

Parenteral Drug Association Training and Research Institute (PDA TRI)

Bethesda Towers, Ste. 150
4350 East-West Hwy.
Bethesda, MD 20814
tel. 301.656.5900
fax 240.482.1659
www.pdatraining.org

Our mission at the **PDA Training and Research Institute (PDA TRI)** is to establish and provide unprecendented worldwide education, training and research opportunities in pharmaceutical and biopharmaceutical sciences and associated technologies. We provide hands-on, intensive, job-focused training you can bring home and apply immediately on the job.

Our broad curriculum is designed for you to enhance your professional development in *aseptic processing, biotechnology, environmental monitoring, filtration, microbiology, quality/regulatory affairs, training, validation and more.* Training courses are held at the PDA TRI facility in Bethesda, Maryland, throughout the United States, and around the world. Courses can also be tailored and brought directly to your organization for on-site training.

Our state-of-the-art training facility includes:

- An aseptic processing suite containing
  - Component prep lab
  - Gowning/degowning areas
  - Clean staging area
  - Filling room
- Biotech lab
- Clean-in-place lab
- Microbiology lab
- Classrooms and student work areas

We have a well-equipped training facility which includes:

- A Fedegari air overpressure/saturated steam autoclave
- Filling line
- Bioreactors/fermenters
- CIP skid
- Continuous particle monitoring system/viable air monitoring
- Laminar flow hoods
- Biosafety cabinets
- Visual inspection booths
- Incubators
- Syringe filler

Our facility is available for your use. TRI makes its training facility available for your use for customized research projects. In addition, we can custom develop any of our training courses to meet your specific needs, either at the Bethesda, MD facility or at your site.

At PDA TRI, we provide skills that can be applied the next day!

PDA®
Parenteral Drug Association
Connecting People, Science and Regulation®

Patheon Inc.

4721 Emperor Blvd, Suite 200
Durham, NC 27703-8580
tel. 866.Patheon (866.728.4366), 919.226.3200
fax 919.474.2269
www.patheon.com

Patheon Inc. (TSX: PTI) is a leading global provider of contract development and manufacturing services to the global pharmaceutical industry. The company provides the highest quality products and services to approximately 300 of the world's leading pharmaceutical and biotechnology companies. Patheon's services range from preclinical development through commercial manufacturing of a full array of dosage forms including parenteral, solid, and liquid forms. Patheon uses many innovative technologies including single-use disposables, Liquid-Filled Hard Capsules and a variety of modified release technologies.

Patheon's comprehensive range of fully integrated Pharmaceutical Development Services includes preformulation, formulation, complex formulation, analytical development, clinical manufacturing, scale-up and commercialization.

The company recently started offering a new line of softgel development and manufacturing services, P-Gels, which is a partnership between Patheon, the world's leading provider of contract development and manufacturing services, and Softigel, part of the Procaps Group, one of the world's largest manufacturers of softgel products.

Patheon's integrated development and manufacturing network of 10 facilities, nine development centers and one clinical trial packaging facility across North America and Europe, ensures that customer products can be launched with confidence anywhere in the world.

Perfex Corp.

32 Case St.
Poland, NY 13431
tel. 315.826.3600
fax 315.826.7471
www.perfexonline.com

TruCLEAN™ Pro

The TruCLEAN™ Pro captures and isolates contaminants, ensuring delivery of unadulterated cleaning and sanitizing agents. No more re-applying dirty water or weakened solutions, experienced with old-style mopping supplies. TruCLEAN™ Pro is compatible with gamma, ETO and autoclave sterilization. Available in double or triple-bucket design.

TruCLEAN™ II

Our unique bucket-in-bucket concept works to isolate soiled contaminants from cleaning and disinfecting agents. Avoid high costs and risk of run-off contaminants common with steam-sterilizers. TruCLEAN™ Components are constructed of high-grade stainless steel, easy to maintain and guaranteed to deliver reliable cleaning results time after time. Clean floors, walls and ceilings with this efficient, compact mopping system. Compatible with gamma, ETO autoclave sterilization.

TruCLEAN™ Sponge Mops

Designed specifically for use in cleanroom and sterile environments, the TruCLEAN™ Sponge Mop is ideal for applying disinfectants and sterilants. This specially formulated polyurethane foam has excellent chemical, microbial and abrasion resistance. TruCLEAN™ Sponge will not release liquids until pressure is applied. Sponge can hold up to 5 times its weight in liquids.

TruCLEAN™ Microfiber Mops

Introducing our line of TruCLEAN™ Microfiber Mops, the most environmentally friendly, non-chemical tool on the market for today's cleaning industry. Our Microfiber Mops can absorb up to 7 times their weight in liquids and can be re-used up to 500 times. Compatible with gamma, ETO autoclave sterilization, also launderable.

PERFEX Squeegees

Our Twin-Blade and Quick-Dry Foam Squeegees are chemically resistant and non-sparking, will not rust or corrode. Quickly wipe surfaces dry and nearly streak-free. Ideal for floor chemical application. The squeegees 100% polymer construction will resist water, oil, grease, detergents, sanitizers and solvents. Wash and rinse with warm water, dries quickly.

PERFEX Push Brooms

Polypropylene fibers are fused onto high-impact resistant polymer block, eliminating fiber fallout. Perfex color-coded brooms, brushes and handles will not absorb bacteria, liquids or odors and are unaffected by water, grease, petroleum products, detergents, sanitizers and solvents. Help avoid cross-contamination in your facility by using Perfex brooms, brushes and handles.

Pfizer CentreSource

7000 Portage Road
Kalamazoo, MI 49001
tel. 269.833.5844
fax 269.833.3604
www.pfizercentresource.com

Leader in Steroid Intermediates and Active Pharmaceutical Ingredients

Pfizer CentreSource has a history of innovative steroid technology stretching back to 1949. Our continued focus on product and process development underscores PCS' long-term commitment to quality steroid APIs and steroid intermediates.

PCS offers customers a reliable supply source for corticosteroids, hormonal steroids, prostaglandin intermediates and other selected chemical products that meet the most exacting quality standards – all with Pfizer's innovative manufacturing technology.

We provide:

- Comprehensive resources for analytical, regulatory, and technical support
- Outstanding chemical and bioprocess expertise and infrastructure
- In-process and finished API analytical methods development
- Comprehensive regulatory/registration file preparation

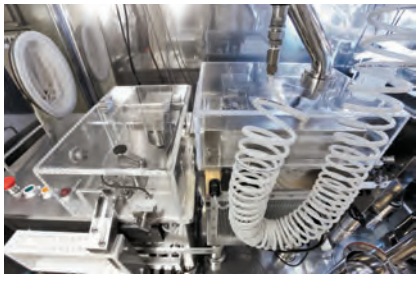
Therapeutic Proteins–Clinical and Commercial Manufacturing

PCS delivers innovative, high quality services that leverage Pfizer's leadership in biologics development and manufacturing across microbial and eukaryotic expression platforms. Among the capabilities available to PCS customers are:

- Rapid technology transfer and scale-up
- Expertise in biological product characterization
- Clinical-scientific and regulatory development know-how
- Biologics manufacturing and supply chain experience
- Extensive drug product and cold chain operations

Some important differences you'll find in working with Pfizer's bioprocessing and development experts:

- Application of Operational Excellence to manufacturing therapeutic proteins
- Regulatory relationships and successful track record second to none
- Highly experienced biotherapeutics professionals
- Emphasis on superior science including new platforms, state of the art facilities and technical expertise.



People, Process, and Packaging

Development, manufacturing and packaging for highly-potent drug product just got a little easier, with a complete, end-to-end suite of High Containment Services from Pfizer CentreSource. With advanced facilities that span the range from our award-winning engineered containment models to segregation-based models, Pfizer CentreSource applies its intensive project management protocols to help get your successful product to market faster. Our solutions run from development support and advanced manufacturing to the point of product use with our unique Cytosafe© packaging

With access to Pfizer's advanced manufacturing infrastructure, PCS offers various technologies and capabilities for high-containment oral solid manufacturing.

- Sieving/Milling/Blending
- High Shear Wet Granulation
- Aqueous Film Coating
- Clinical Scale to Commercial Scale (up to 700kg)
- Complex Packaging Capabilities
- Blister, Bottle, and Carding/Wallet Packaging
- Break-resistant Cytosafe Vials
- Dry Granulation
- Core Compression
- Encapsulation

Pharma Tech Industries

545 Old Elbert Rd.
Royston, GA 30662
tel. 706.246.3555
fax 706.246.3330
www.pharma-tech.com

PHARMA TECH INDUSTRIES
Outsourcing done right.®

Description

The largest pharmaceutical contract manufacturer and packager of powder products in the world, Pharma Tech Industries (PTI) has been serving the needs of leading global pharmaceutical and personal-care companies with product development, manufacturing, and packaging services for more than 35 years. PTI currently serves more than a dozen clients in two facilities and produces more than 300 SKU's of powders, effervescent, and solid-dose products, as well as cotton swabs and injection-molded components.

Facilities

With strategically located, fully integrated facilities in Royston, GA and Union, MO, Pharma Tech Industries has more than 360,000 square feet of combined cGMP development, manufacturing and packaging space. This includes nine ISO 8 Design clean rooms for the manufacturing and packaging of Rx and NDA products, full analytical and microbial laboratories for on-site testing, and a dedicated machine tool shop.

Services

Pharma Tech Industries controls the supply chain process of pharmaceutical products through turnkey services:

- Contract manufacturing, including powder blending, solid-dose compression, effervescent products, and cotton swab manufacturing
- Contract packaging, including bottle filling, stick packs, pouch (unit dose) filling, cartoning, labeling and custom packaging
- Contract molding of caps, bottles, components and devices through injection molding, single- and bi-component injection molding, compression molding and profile extrusion
- Technology transfer, including transfer of late stage R&D, transfer of dedicated large- and small-scale operations, transfer of niche processes, and transfer of PTI's turnkey approach through vertical integration
- On-site, full-scale testing with both microbial and analytical capabilities

Recent Developments

- PTI stood out among 67 CMOs to be named *Best Overall Supplier* by one of the world's five largest pharmaceutical companies. Criteria included quality, customer service, supplier collaboration, responsiveness to client needs, inventory management and financial collaboration.
- PTI completed its ninth ISO 8 Level (Class 100,000) clean room. The specially engineered rooms have highly-sensitive control features to closely regulate and monitor both temperature and humidity. PTI services using clean rooms include unit dose/pouch filling, compounding, and blending of powder-based products.
- PTI has broadened its list of contract molding capabilities. PTI can mold bottles, caps, healthcare packaging components, and medical devices spanning a range of contract molding assignments–from simple to complex, and from low- to high-volume. Comprehensive projects through PTI can drastically reduce lead times and speed to market while reducing costs associated with supply chain coordination and transport.

Sartorius Stedim North America

5 Orville Drive
Bohemia, NY 11716
tel. 800.368.7178
fax 631-254-4253
www.sartorius-stedim.com

FlexMoSys™

Sartorius Stedim Biotech's single-use and reusable product portfolio and G-Con Manufacturing's modular and mobile cleanroom "pods" combine to provide an unparalleled set of cost-effective, "plug and play" tools for next-generation biomanufacturing. Its production capacity is fast, fully integrated and ready-to-use.

Sartopore® Platinum

Sartopore® Platinum represents a new class of Sterile Filtration offering exceptional total throughput performance with minimal protein binding, easy wettability prior to Integrity Testing, and dry and reverse steambility for cartridges. The overall Cost of Ownership for filtration is reduced for many challenging applications due to its unique nature.

BIOSTAT B

BIOSTAT® B is the most successful autoclavable laboratory fermentor system in its class, now available in a third generation. Configurations support cell culture plus microbial fermentation. One or two reactors can be controlled independent of each other. The unit can be combined with our stirred-glass (1–10L) or single-use (2L) vessels.

Biowelder TC

The BioWelder® TC is a fully automated device for connecting thermoplastic tubing in a sterile welding operation. This new, innovative technology allows sterile connection of liquid filled tubing from 5/8'' up to 1'' outer diameter. Safe and robust, the BioWelder® TC has been intensively qualified and is supported by a Validation Package upon request.

Sartobind STIC

Sartobind® STIC membranes are a new group of Salt Tolerant Interaction Chromatography membrane adsorbers. They bind negatively charged impurities such as viruses, DNA and HCP at much higher salt concentrations than Q matrices. The single-use product reduces validation cost, consumption of buffers, footprint, and speeds up time to market.

CONFIDENCE® Validation Services

Sartorius Stedim Biotech's Validation Services provides extractable and leachable testing that is designed to meet current regulatory requirements. Our recommended approach includes the use of at least two orthogonal analytical techniques—for example, GC-MS in addition to HPLC-UV. Let us help you implement a successful test strategy. Contact us today!

Schenck AccuRate

746 E. Milwaukee Street
Whitewater, WI 53190
tel. 262.473.2441
fax 262.473.4384
www.accuratefeeders.com

PureFeed® DP-4 Feeder

The PureFeed® DP-4 is a highly innovative gravimetric feeder that can accurately meter dry pharmaceutical, nutraceutical, and cosmetic powders at feed rates as low as 20 grams / hour. Jet milling, continuous blending, medical-grade plastics compounding, packaging, coating, and ingredient weighing are applications ideally suited for the DP-4.

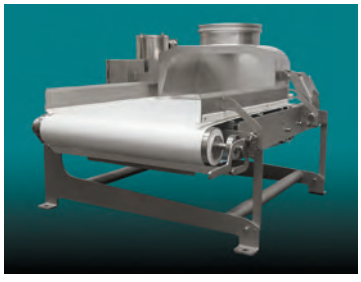
A key feature of the PureFeed® DP-4 is a speed controlled, inert ceramic feed disc. Positioned at the base of a cylindrical, electropolished stainless steel material storage chamber, the disc rotates to precisely discharge tiny amounts of material, continuously and pulsation free over a 20 to 2,000 gram feed rate range.

The PureFeed® DP-4 is currently installed in pharmaceutical processing applications for feeding SAP, Mannitol, Naproxen, Maltrin-Maltodextrin, and others.

PureFeed® AP-300 Feeder

The Schenck AccuRate PureFeed® AP-300 feeder was designed specifically for pharmaceutical processes that include the following customer driven features; quick and easy disassembly, a dual arm agitation system for maximizing material handling versatility, and an FDA compliant EPDM feed hopper that is disposable and recyclable. That means simpler, shorter cleaning cycles and virtually, no chance of cross contamination when moving from one material to another.

The PureFeed® AP-300 is available in volumetric and gravimetric configurations for pharmaceutical and nutraceutical applications involving feed rates from 0.5 to approximately 150 Kg / hour.



DEA Sanitary Open Frame Weighbelt

The DEA Open Frame Weighbelt Feeder is designed specifically for sanitary process applications. Unique features include tool-less, rapid belt removal for frequent cleaning cycles, an IP69K stainless steel load cell manufactured to withstand high pressure spray, a shaft mounted, wash-down drive system for simple power transmission, and product contact surfaces with 316 stainless steel.

The DEA Open Frame Weighbelt Feeder provides weight controlled feeding, weight indication and totalization for fragile materials like tablets or capsules. Like other Schenck AccuRate DEA Weighbelt Feeders the sanitary open frame is offered in models with 12” and 24” belt widths, BIC (belt weight influence compensation), and accuracies of ± 0.25% to 1% of set rate sigma.

Shimadzu Scientific Instruments

7102 Riverwood Drive
Columbia, MD 21046
tel. 800.477.1227
fax 410.381.1222
www.ssi.shimadzu.com

Nexera MP UHPLC

The Nexera MP UHPLC is ideally suited as a front end for all LCMS platforms. It utilizes the SIL-30ACMP Multiplate Autosampler, which features a high-speed injection (7 seconds), near-zero carryover (0.0015% or less), and enables up to 6 microtiter plates to be loaded at once.

LCMS-8040 Triple Quadrupole LC-MS/MS

Utilizing proprietary high-speed technologies, with enhanced sensitivity even at faster scan speeds, Shimadzu's LCMS-8040 maximizes throughput. Newly improved ion optics maintain signal intensity and suppress crosstalk, even for high-speed or simultaneous multi-component analysis. This increases sensitivity for MRM and scan mode measurements, expanding the application range & ensuring high-throughput analysis at lower levels of detection.

Laboratory TOC Analyzers

From inspections of the water used in drug manufacture to cleaning validation, Shimadzu's TOC analyzers are ideally suited for the measurement of residual pharmaceutical products and their constituent substances. They feature ultra-wide measurement range, patented 680°C Combustion Catalytic Oxidation/NDIR detection method, fully automated sample pretreatment, and multiple autosampler options.

UV-1800 UV-Vis Spectrophotometer

In addition to the highest resolution (1 nm) and smallest footprint of all standalone UVs in its class, Shimadzu's UV-1800 features a wavelength range of 190 to 1100 nm, enhanced instrument validation, security, & maintenance functions, reduced stray light & noise levels, and a variety of measurement modes.

SALD-2300 Particle Size Analyzer

The SALD-2300 provides continuous measurement in real time, at minimum one-second intervals, and its measurement range spans particle sizes from 17 nm to 2,500 µm. It comes with WingSALD II software, the world's first to automatically calculate an appropriate refractive index based on the light intensity distribution reproduction method.

Analytical Balances

Shimadzu balances deliver the performance, functionality, and value scientists need. The unique UniBloc one-piece manufacturing assembly assures stable temperature characteristics, excellent response, and a long operational life, while Windows® Direct Communication enables easy integration of weighing results with laboratory software.

Stäubli Robotics

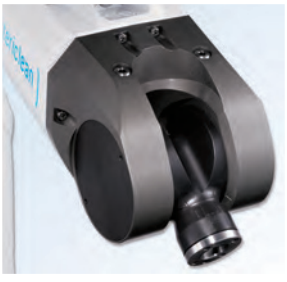
201 Parkway West
Duncan, SC 29334
tel. 864.430.1980
fax 864.486.5497
www.staublirobotics.com

New Stericlean Robot

Thanks to its experience in the field of Life Science and the requirements of a leader in the Pharmaceutical industry, Stäubli has adapted its range of well known CLEANROOM industrial robots to meet the stringent requirements of the Vapor Hydrogen Peroxide decontamination process.

Stericlean Robot Highlights:

- Fully hydrogen peroxide (H202) resistant robot
- Robot arm suitable for decontamination process in VHP environments
- Human arm like automated operator in isolator environment (glove box)
- Reliability proven by the leaders in life science and Cleanroom



Stericlean Robot Technical features:

- Special surface treatments of the TX 60 Stericlean robot arm
- Critical parts in stainless steel
- Specific lip seals
- System and user connections protected under the base of the robot
- Small footprint with large work envelope
- GMP (Good Manufacturing Processes) qualified

Stericlean applications:

- Pharmaceutical Industry, Life Science, and Medical Technology industries
- Lab operations
- Batch testing
- Production
- Drug discovery

TX Stericlean was born from a strong relationship between Stäubli, a system integrator and our end user. These committed partners share the same strategies and bring to the table experience in robotics, automation processes and “clean room” environments.

Whether in industrial production, cell culture or medical preparation, this new technology has demonstrated its ability to simulate human motion and meet productivity goals, significantly raising the rate at which syringes can be filled on a high-speed line.

Veltek Associates, Inc.

15 Lee Blvd.
Malvern, PA 19355-1234
tel. 610.644.8335, fax 610.644.8336
vai@sterile.com
www.sterile.com

SimpleMIX system

The "SimpleMIX System" eliminates filter sterilizing of disinfectants and sporicides. A sealed multichamber container mixes both solutions. The top part contains the sterile concentrated disinfectant, and the bottom section accommodates the sterile USP water-for-injection-quality water. This system ensures the appropriate dilution is made in a closed sterile system each time.

Peracetic acid

Veltek offers the "DECON SPORE 200 Plus" peracetic acid–hydrogen peroxide solution for the sterilization of manufacturing, packaging, and filling equipment. The product has less odor than ready-to-use sterilants and requires 80% less storage space. It is available in 1-gal containers, unit-dose bottles, and in the "SimpleMix" system.

Hands-free dispensing system

Veltek offers the "Asepti Cleanse Hands-Free" dispensing system to dispense sterile alcohol and hand sanitizer. The Asepti Cleanse system is a sealed, water-resistant unit designed to meet the requirements of cleanroom operations. The unit can be powered by either four D-cell batteries or connected directly to a 110-V power source.

Easy2Gown System

Veltek Associates, Inc.'s Easy2Gown garments offer an innovative fold which allows the gown to be easily donned with virtually no operator contact with the outside of the gown. All Easy-2Gown garments are packaged using a unique patented fold which was developed to minimize operator error and personal contact from the outside of the gown during the gowning process. Operators have fewer manipulations while donning the Easy2Gown garments.

Cage2Wash®

Cage2Wash products have been specifically designed for critical animal facility component and animal cage washing applications. In this venue, the appropriate use of a cleaning agent to remove animal waste and animal by products is critical.

Process2Clean®

Process2Clean products have been specifically designed for critical clean in place applications. In this venue, the appropriate use of clean in place cleaners warrants two concerns. The first concern relates to the ability of the specific detergent to remove existent product residues that may exist in either open or closed processes manufacturing equipment and vessels. The second concern is the ability to rinse free the product residue, P2C addresses both concerns with ease.

Watson-Marlow Pumps Group

37 Upton Technology Park
Wilmington, MA 01887
tel. 800.282.8823
fax 978.658.0041
support@wmpg.us
www.wmpg.com

Flexicon FF15 Filling System

Flexicon's FF15 peristaltic filling system is compact enough to fit in the tight space of a biosafety cabinet. The vial filling system uses new Flexicon asepticsu single use fluid path technology to simplify validation and deliver effortless changeover for a variety of fills.

PureWeld Tubing

PureWeld XL tubing is designed for high purity and secure peristaltic pumping. A high-quality weldable tube capable of completely secure welding, PureWeld XL allows for connector-free fluid paths to be assembled in just minutes. Test results show that PureWeld allows for the least internal spallation when compared to other weldable tubing.

Watson-Marlow Pumps for Downstream Process and Purification

Whether selecting equipment for R&D, process development, or manufacturing, engineers around the world recognize Watson-Marlow pumps for our high quality, reliability, and performance. Offering contamination-free pumping with a sterile single-use flow path, Watson-Marlow's peristaltic technology simplifies cleaning validation and enhances the integrity of downstream processes and purification.

Watson-Marlow 120

Watson-Marlow's 120 laboratory peristaltic pumps are ideal for biopharm, science, research, and OEM applications. Features and benefits include a compact footprint that saves bench space, exceptional speed control and accuracy, a new flip-top 114 pumphead, and simple intuitive operations.

Flexicon Filling and Capping System

Flexicon offers a new high-throughput peristaltic filling and capping system. Using high precision peristaltic filling technology and Flexicon's aseptic**su** single-use fluid path, Flexicon's filling and capping system ensures purity and simplifies validation. Featuring fully automated setup, changeover for different vials is quick, safe and achievable within 10 minutes.

Flexicon PF6 Peristaltic Filling Machine

Flexicon benchtop peristaltic fillers are designed for use in cleanrooms for production processes complying with cGMP. Batch set up is achieved in one minute with fill volumes from 5 ml to 5 liters and precise ±0.5 dosing accuracy. Offering a contamination-free single-use flowpath, Flexicon's peristaltic technology simplifies cleaning validation and enhances the integrity of high purity upstream processes, purification, and fill/finish applications.

Weiler Engineering, Inc.

1395 Gateway Drive
Elgin, IL 60124
tel. 847.697.4900
www.weilerengineering.com

Weiler Engineering, Inc.

The corporate focus of Weiler Engineering, Inc. is to provide the most advanced aseptic liquid processing technology available through the application of customized ASEP-TECH® Blow/Fill/Seal machinery and integrated services. Weiler's 140,000 ft², state-of-the-art manufacturing and corporate facility is conveniently located near O'Hare International Airport in Chicago, IL USA.

ASEP-TECH® Model 624 Blow/Fill/Seal Machine

The Asep-Tech® Model 624 Blow/Fill/Seal machine is designed as an entry level machine to meet flexible manufacturing or research and development requirements. Featuring easy maintenance and low operating cost, the versatile Model 624 can produce sterile, liquid filled, tamper-evident containers ranging in size from 0.5mL up to 500mL.

ASEP-TECH® Model 628 All-Electric Blow/Fill/Seal Machine

Weiler Engineering, Inc. introduces the new all-electric version of the popular Model 628 Blow/Fill/Seal machine. The all-electric model offers the ultimate in clean, green processing, minimizing the carbon footprint and enhancing the quality of the processing environment through highly reduced particulate generation. The all-electric option is ideal for injectable product applications.

ASEP-TECH® Model 640 Blow/Fill/Seal Machine

The high output Model 640 machine is designed for maximum flexibility to meet today's demanding FDA and EU processing requirements. It features a two-piece stepped base to facilitate easy maintenance and comes with an electronic fill system and digital controls to enable performance to tight fill tolerances in critical applications.

ASEP-TECH® Model 603 Blow/Fill/Seal Machine

The Asep-Tech® Model 603 Blow/Fill/Seal machine is designed for production of Large Volume Parenteral products (LVPs). It features a two-piece stepped base design for easy maintenance and convenient product discharge and is designed to produce sterile, liquid filled, tamper-evident containers ranging in size from 200mL up to 1000mL, in full-scale production quantities.

ASEP-TECH® Model 660 Blow/Fill/Seal Machine

The Asep-Tech® Model 660 Blow/Fill/Seal machine is the latest addition to a proven line of sterile liquid pharmaceutical packaging machines from Weiler. The Model 660 is a high-output machine, designed to produce sterile, liquid filled, tamper-evident containers ranging in size from 200mL up to 1000mL.

WireCrafters, LLC

6208 Strawberry Lane
Louisville, KY 40214
tel. 800.626.1816
fax 502.361.3857
www.wirecrafters.com

DEA Approved Drug Storage Cages

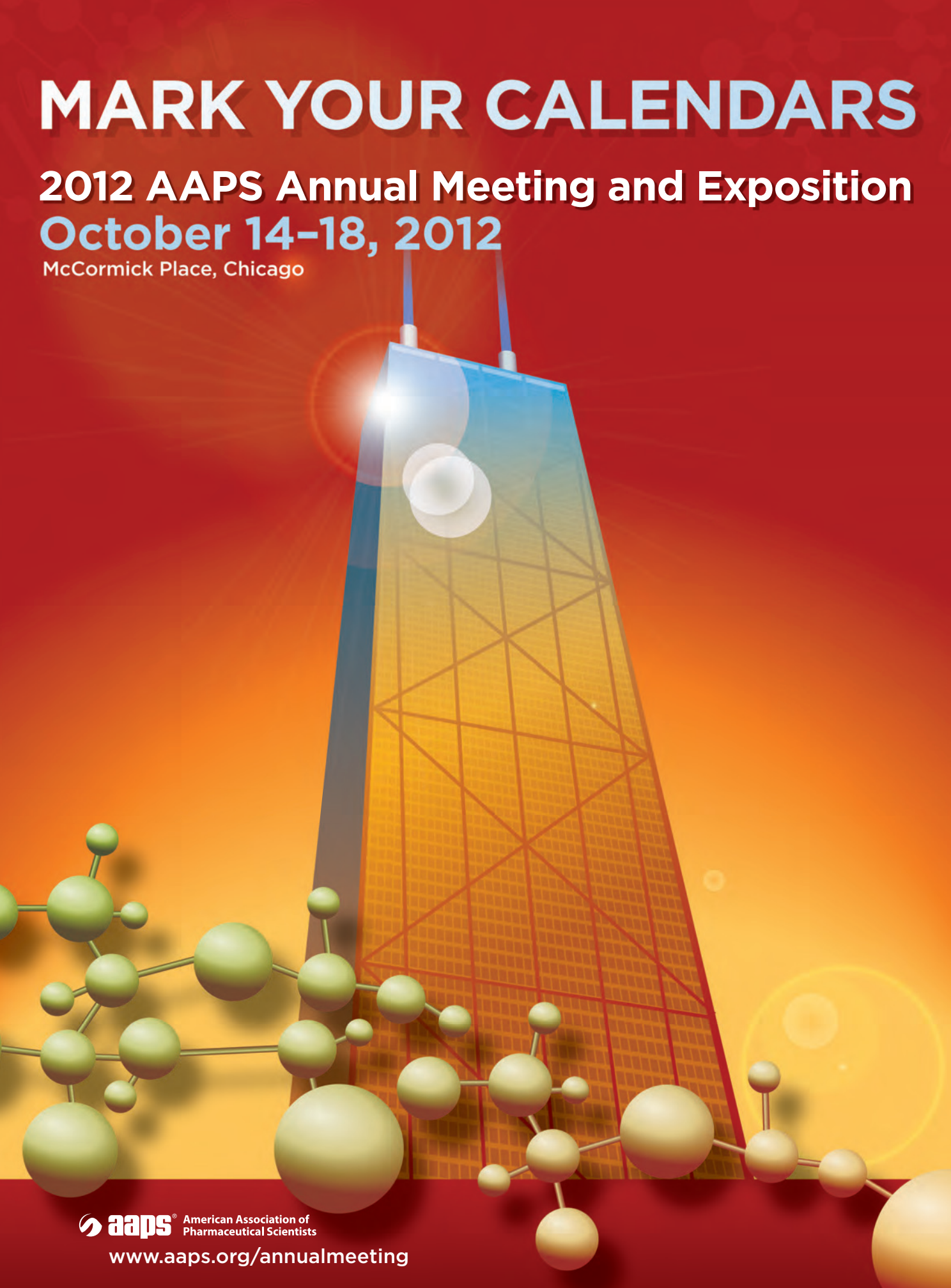
When properly installed, WireCrafters' Style 840 Partitions meet the US Drug Enforcement Administration's (DEA) requirements for physical security of Schedule III through V controlled substances as outlined in Title 21 CFR Sections 1301:72-1301.76 physical security controls. This drug storage application of WireCrafters wire partitions is ideally suited for pharmacies, pharmaceutical companies, medical facilities, distribution centers, record storage, drug warehouses, and much more.

MARK YOUR CALENDARS

2012 AAPS Annual Meeting and Exposition

October 14–18, 2012

McCormick Place, Chicago



aaps® American Association of Pharmaceutical Scientists

www.aaps.org/annualmeeting

MANUFACTURING EQUIPMENT & SUPPLIES

Double planetary mixers

Ross has introduced new double planetary mixers with a slightly tilted configuration for more effective and complete discharge of flowable products. The mixers are intended for use in the preparation of pastes and gels, as well as granulations and free-flowing dried powder blends. **Ross, Charles & Son Company,** *Hauppauge, NY • www.mixers.com • tel. 800.243.ROSS*

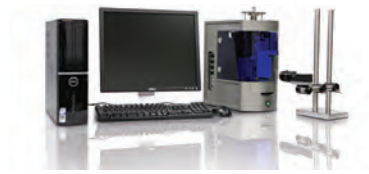
Single-use systems brochure

Meissner has released its new capabilities brochure featuring fluid-handling and management solutions delivered by the One-Touch single-use systems portfolio. The brochure gives an overview of each of the primary products within the single-use portfolio, including TepoFlex PE and FluoroFlex PVDF biocontainer assemblies. The brochure also discusses the documentation available for the One-Touch portfolio including the biocontainer assembly "Standards Guides." **Meissner Filtration Products,** *Camarillo, CA • www.meissner.com • tel. 805.388.9911*

Tablet-compression accessories catalog

Natoli's new tablet-compression accessories catalog allows the functionality to browse products and quickly request quotes online. The catalog offers customers the capability to flip through the pages of the digital catalog, click items to add to a virtual "Quote Cart" feature, and checkout upon completion. Visit natoli.com/catalog.html. **Natoli Engineering Company,** *St. Charles, MO • www.natoli.com • tel. 636.926.8900*

MANUFACTURING EQUIPMENT & SUPPLIES



Visual-observation tool

The APK visual-observation tool is suitable for random-sampling manual inspection. Users can program spin speed according to liquid viscosity or container diameter, thus providing repeatable rotation speed and duration for inspected containers. The APK allows the human eye to detect foreign particles easily. **Eisai Machinery USA,** *Allendale, NJ • www.eisaiusa.com • tel. 201.746.2111*

Fluid-bed dryer bags

Kavon provides custom replacement fluid-bed dryer bags for US and European equipment models. The bags are appropriate for wet granulation, dry filtration, and wet and dry coating applications. The company offers flexible 1–4-bag systems in various fabrics choices and also repairs bags. **Kavon Filter Products,** *Wall Township, NJ • www.kavonfilter.com • tel. 732.938.3135*

Pharmaceutical feeder

The Schenck AccuRate PureFeed AP-300 feeder was designed specifically for pharmaceutical processes. The feeder is designed for quick and easy disassembly. Each unit incorporates a dual-arm agitation system for maximizing material handling versatility and a disposable, FDA-accepted EPDM feed hopper. Feed rates range from 0.5 to 150 kg/h. **Schenck AccuRate,** *Camarillo, CA • www.accuratefeeders.com • tel. 800.558.0184*

MANUFACTURING EQUIPMENT & SUPPLIES

Top-entering agitators

The PharMix Series 3000 and 4000 top-entering agitators are specifically designed for demanding pharmaceutical and biotechnology mixing applications. The units' robust shaft designs run in free air for cleaning in place and eliminate the need for stabilizing rings. Each agitator comes with a complete prevalidation documentation package. **DCI,** *St. Cloud, MN • www.dciinc.com • tel. 320.252.8200*

Weigh pan

The SmartGrid weigh pan is designed for Mettler Toledo's Excellence balances. The weigh pan is designed to minimize the effects of air turbulence for faster stabilization. Users can secure fastening and direct weighing into tare containers with Ergoclips. The unit is intended to provide quality and durability. **Mettler Toledo,** *Columbus, OH • www.mt.com • tel. 800.METTLER*

Weldable tubing

Watson-Marlow's PureWeld XL is a thermoplastic elastomer tubing intended for use in sanitary environments in pharmaceutical and biotechnology processing applications, from research to production including cell media and fermentation, sterile filling and dispensing, high-purity water transfer, vaccine production, fluid transfer, and filtration. PureWeld XL meets full biopharmaceutical testing standards, including FDA requirements and USP Class VI certification. **Watson-Marlow Tubing,** *Wilmington, MA • www.wmtubing.com • tel. 800.282.8823*

MANUFACTURING EQUIPMENT & SUPPLIES

Rheometer

Brookfield's R/S Plus rheometer with direct-yield stress measurement is designed for quality control and research applications. The R/S unit has high flow-measurement capability, an increased speed range (i.e., 0.1 to 1000 rpm), control solution, and measurement sensitivity. The encoder is designed to provide control at low torque and shear rates, a precise static yield test capability, and more information for creep testing. **Brookfield Engineering Laboratories,** *Middleboro, MA • www.brookfieldengineering.com • tel. 800.628.8139*

Filter-integrity tester

Thirty years of design refinements have resulted in the Sartocheck 4 plus advanced filter-integrity tester. The unit incorporates productivity- enhancing features and is built to be durable. The device also was designed for the operator's ease of use. **Sartorius Stedim North America,** *Bohemia, NY • www.sartorius.com • tel. 631.254.4249*

Pharmaceutical robot

The Stericlean robot automates processes in isolator and cleanroom environments. Designed to protect staff and products, the robot fully withstands decontamination with vapor hydrogen peroxide. Stäubli Robotics offers various solutions for aseptic automation. **Stäubli Robotics,** *Duncan, SC • www.staubli.com • tel. 800.257.8235*

MANUFACTURING EQUIPMENT & SUPPLIES

Tablet press

The new model of the Hata CVX Core Press enables precision core alignment and multilayer core tableting. The custom mechanical assembly, an addition to Hata's Three-Layer Tableting Press, is specific to customers' core tablet sizes and shapes. The CVX-Series is suitable for multilayer and custom core-tableting technology. **Elizabeth-Hata,** *McKeesport, PA • www.eliz.com • tel. 412.751.3000*

Aseptic liquid-sampling system

GEMÜ offers a fully automatic aseptic sampling system for liquids and pure steam. The system is appropriate for mobile or fixed installation. It features sterile sampling and transport and programmable automation for customer-specific variables. The closed system protects personnel and uses compressed air as cooling and condensing media. **GEMÜ Valves and Instrumentation,** *Atlanta, GA • www.gemu.com • tel. 404.344.8970*

Automated sampling system

Allegheny Bradford designed its Automated Sampling System to be easy to install, operate, and maintain. The system's continuous-flow design ensures constant sterility that supports cleaning and steaming in place. The unit includes a double-tubesheet heat exchanger for leak detection and Pitot–Venturi tube design. **Allegheny Bradford,** *Lewis Run, PA • www.alleghenybradford.com • tel. 800.542.0650*

OUTSOURCING & CONSULTING SERVICES

ONE 2 ONE™

Parenteral Contract Manufacturing Service of Hospira

Contract-manufacturing services

Hospira's One 2 One business specializes in contract manufacturing of injectable products packaged in vials, prefilled syringes, cartridges, flexible containers, and ampoules. Additional offerings include product development and fill–finish of clinical trial materials, registration, and commercial batches. The company's range of capabilities spans biologics, potent drugs, vaccines, cytotoxics, controlled substances, and lyophilization. **Hospira One 2 One,** *Lake Forest, IL • www.one2onecmo.com • tel. 224.212.2267*

Cytotoxic contract manufacturing

An eight-page brochure describes Baxter's cytotoxic manufacturing facility in Halle, Germany. It includes information about cytotoxic contract manufacturing using barrier-isolator technology and services such as lyophilization, liquid-vial filling, dry-powder filling, and sterile crystallization. The facility manufactures for distribution markets, including the United States, Europe, and Japan. **Baxter BioPharma Solutions,** *Round Lake, IL • www.baxterbiopharmasolutions.com • tel. 800.422.9837*

Metrics INC.

Contract services

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Pharma Tech Industries offers a brochure that describes its pharmaceutical manufacturing and packaging services, its facilities in Georgia and Missouri, and its technical capabilities. The brochure also includes customer testimonials from global pharmaceutical leaders and photos of its facilities, machinery, and dedicated employees. **Pharma Tech Industries,** *Royston, GA • www.pharma-tech.com • tel. 706.246.3555*

CLEANROOM EQUIPMENT & SUPPLIES

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Microfiber mops

Perfex offers a line of TruCLEAN microfiber mops, which are nonchemical cleaning tools designed to be environmentally friendly. The microfiber mops can absorb as much as seven times their weight in liquids and can be reused as many as 500 times. The washable products are compatible with gamma irradiation, ethylene oxide, and autoclave sterilization. **Perfex,** *Poland, NY • www.perfexonline.com • tel. 800.848.8483*

PACKAGING EQUIPMENT & SUPPLIES

Blow–fill–seal machine

The Asep-Tech Model 628 blow–fill–seal machine from Weiler features a two-piece stepped base design to facilitate maintenance and product discharge. Model 624 tooling can be used on the Model 628 machine. The Model 628 unit produces sterile, liquid-filled, tamper-evident containers ranging in size from 0.5 mL to 250 mL. **Weiler Engineering,** *Elgin, IL • www.weilerengineering.com • tel. 847.697.4900*

Transfer packaging for prefillable syringes

BD TSCF packaging ensures the secure transfer of sterile prefillable syringe components into the pharmaceutical filling environment. The packaging is compatible with IDC Biosafe doors for aseptic filling machines within isolator or barrier systems. This packaging is part of the BD SCF global offer, which features expertise in sterile processing of preservative-free drugs; secure, reliable, easy-to-use systems; and drug master files and technical dossiers. **BD Medical–Pharmaceutical Systems,** *Franklin Lakes, NJ • www.bdpharma.com • tel. 800.225.3310*

PACKAGING EQUIPMENT & SUPPLIES

Packaging solution

The NextBottle package from Catalent and One World Design and Manufacturing Group is designed to improve patient compliance. The product's dial mechanism dispenses one pill at a time and automatically reminds patients of the last day that a pill was taken. **Catalent Pharma Solutions,** *Somerset, NJ • www.catalent.com • tel. 866.720.3148*

LABORATORY EQUIPMENT & SUPPLIES

On-line TOC analysis

To help pharmaceutical companies improve quality and reduce costs, GE Analytical Instruments offers a science- and risk-based program for achieving real-time release of pharmaceutical water. The program streamlines a complex process and helps companies move total organic carbon testing from the laboratory to the production floor in approximately six months. **GE Analytical Instruments,** *Boulder, CO • www.geinstruments.com • tel. 800.255.6964*

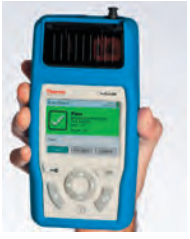
Laboratory blenders

MaxiBlend and MiniBlend laboratory blenders are available in sizes from 0.5 to 16 qt. The units are made of 316-L stainless steel and supplied with V-shells, bins, or double cones. The units feature a tabletop design and include programmable logic controls and safety-interlocked guards. **GlobePharma,** *New Brunswick, NJ • www.globepharma.com • tel. 732.819.0381*

LABORATORY EQUIPMENT & SUPPLIES

Drug-storage system

WireCrafters's Drug Enforcement Agency (DEA)-Approved Storage Brochure shows how WireCrafters Style 840 Partitions meet or exceed DEA special requirements for storage of Schedule III–V controlled substances. Its secured-storage system is designed to be cost-effective. **WireCrafters,** *Louisville, KY • www.wirecrafters.com • tel. 800.626.1816*



Handheld analyzer

Thermo Scientific's TruScan RM unit is a handheld analyzer designed for rapid identification of raw materials and finished-product inspection. The instrument weighs less than 2 lb. and delivers results five times faster than the previous model. A new optical platform enables the TruScan RM unit to identify a broader range of chemical compounds. **Thermo Scientific,** *Wilmington, MA • www.thermoscientific.com • tel. 978.642.1132*

Process-analysis system

FOSS NIRSystems's ProFoss is available with Vision software for pharmaceutical- and chemical-process applications. ProFoss is a process-analysis system based on high-resolution diode array technology. It provides nondestructive analysis of pharmaceutical and chemical products directly in the process line without bypass. The solution helps to optimize the use of raw materials and to consistently run production closer to target specifications. **FOSS NIRSystems,** *Laurel, MD • www.foss-nirsystems.com • tel. 301.680.9600*

LABORATORY EQUIPMENT & SUPPLIES

Analytical system

The amaZon PowerPack liquid chromatography–mass spectrometry system combines the performance and reliability of the amaZon SL ion-trap mass spectrometer with a state-of-the-art Dionex UltiMate 3000 ultrahigh-performance liquid chromatography system. The instrument is designed to enhance the analytical capabilities and productivity of laboratories that analyze the structure of various molecules. **Bruker Daltonics,** *Billerica, MA • www.bdal.com • tel. 978.663.3660*

INFORMATION TECHNOLOGY

Compliance software

EtQ's FDA Compliance Management software is an integrated quality- and compliance-management system designed to maintain compliance to various regulatory requirements and adapt to business processes. EtQ's modules are tightly integrated to deliver a high-quality FDA-compliance solution and include MedWatch Plus, Complaint Handling, Corrective And Preventive Action, Document Control, and Change Management. **EtQ,** *Farmingdale, NY • www.etq.com • tel. 800.354.4476*

Materials-identification database

The PDF-4/Organics 2011 database, featuring 436,901 entries, is designed for rapid materials identification and targeted to the pharmaceutical and specialty-chemical industries. Its design allows for easy interface with diffractometers and data-analysis systems of leading software developers and manufacturers of X-ray equipment. The database is useful for scientists working in consumer products, catalysis, forensic science, analytical laboratories, and production. **International Centre for Diffraction Data,** Newtown Square, PA • www.icdd.com • tel. 610.325.9814

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another heparin-like tragedy. Improving the safety of drugs throughout the supply chain will come at great expense and will only succeed through the diligence of all stakeholders. FDA must be attentive with its drug approval and inspection procedures, and drug producers must remain committed to manufacturing drug ingredients governed by cGMPs. The pharmaceutical industry becomes more global each day, and it becomes increasingly clear that all manufacturers must work to implement quality programs.

As the law is implemented in stages over the next few years, the hope is that the industry will see results from these major steps taken to safeguard the drug supply. The ongoing dialogue between drug manufacturers and FDA has led to a path forward that can hopefully ease the minds of consumers. However, there is more work to be done. Currently, foreign over-the-counter (OTC) drug manufacturing is not being inspected, nor is their inspection included in the passage of the FDA Reform Act. Hopefully, a risk-based inspection approach will be applied to OTC products as well in the future.

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Enactment of FDA Reform Act Improves Drug Safety

John DiLoreto, SOCMA

New law provides FDA with the resources it needs to safeguard drug supply chain.

The bipartisan enactment of the Food and Drug Safety and Innovation Act, signed into law on July 9, 2012, is an important achievement in FDA's objective to ensure the efficiency and quality of drugs manufactured and distributed in the US and abroad. For generic drugs, the legislation makes it possible for the federal government to increase foreign facility inspections, speed approval of lifesaving medicines, reduce drug shortages, and improve the quality and availability of drug ingredients.

A risky market

In the past, the US drug supply has been susceptible to sub-par quality drugs due to the lack of enforcement of basic drug quality inspections of foreign facilities—leading to lax quality compliance standards. According to FDA, approximately 80% of APIs are imported, primarily from high-risk regions, such as Asia (1, 2). FDA has been unable to accurately identify all foreign facilities manufacturing drugs entering the US, and the agency does not have the resources or systems in place to track such foreign facilities for the purpose of quality inspections.

Although domestic pharmaceutical companies can expect an FDA inspection every two to three years, most of their foreign counterparts have never been inspected by FDA. According to a 2010 GAO report (3), it would take FDA, with current resources, more than nine years to inspect all foreign facilities just once. The lack of routine risk-based inspection of foreign facilities endangers the safety of the global drug supply chain, encourages non-domestic job growth, and has the potential of becoming a national security issue.

The ongoing dialogue between drug manufacturers and FDA has led to a path forward.

FDA gains resources

With the passage of the FDA reform bill, the agency indicated in negotiations with stakeholders that it will have the resources it needs to inspect all foreign and domestic generic-drug production facilities with regularity (4).

Inspections will be performed on a risk basis, focusing on the facilities posing the greatest risk to the supply chain. This will provide greater confidence in the safety of generic drugs imported from developing countries.

Members of the Bulk Pharmaceuticals Task Force (BPTF), an industry trade organization of drug ingredient makers within the Society of Chemical Manufacturers and Affiliates, will be among those paying FDA nearly $1.5 billion over the course of five years to accomplish these goals. The Generic Drug User Fee Act (GDUFA), which was negotiated last year by BPTF members and other industry trade groups, is included in the FDA Reform Act. GDUFA will expedite the availability of more affordable, high-quality generic drugs; enhance FDA's ability to prevent substandard and misbranded drugs from entering the supply chain; and level the playing field between foreign and domestic firms.

Significantly, the legislation also authorizes FDA to confiscate and destroy counterfeit, adulterated, or misbranded drugs that enter the US rather than returning them to foreign manufacturers. Past practices forced FDA to send the drugs back to their country of origin, where they were ultimately returned to the drug supply chain in other countries.

Industry and FDA collaborate

Among the most significant but least-known developments contributing to this legislative success is the fact that, at a time when company budgets are tight and economic uncertainty runs high, generic-drug producers voluntarily agreed to pay these fees to avoid

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John DiLoreto is executive director of the Bulk Pharmaceuticals Task Force, an affiliate organization of the Society of Chemical Manufacturers and Affiliates (SOCMA).

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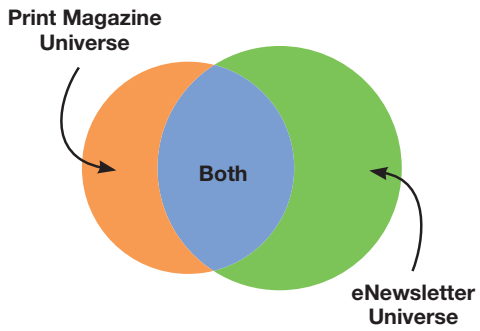

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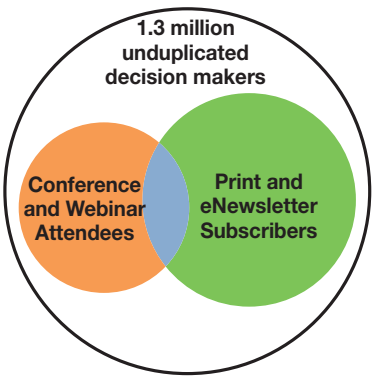

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