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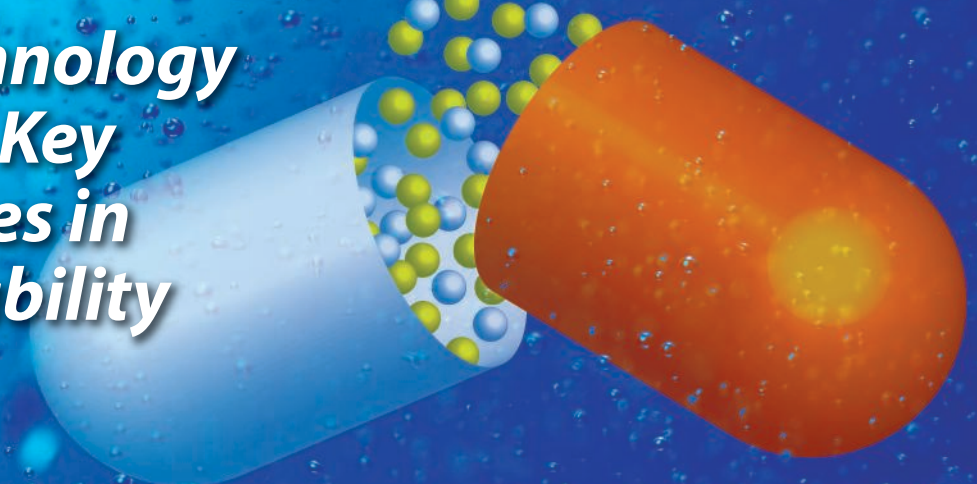

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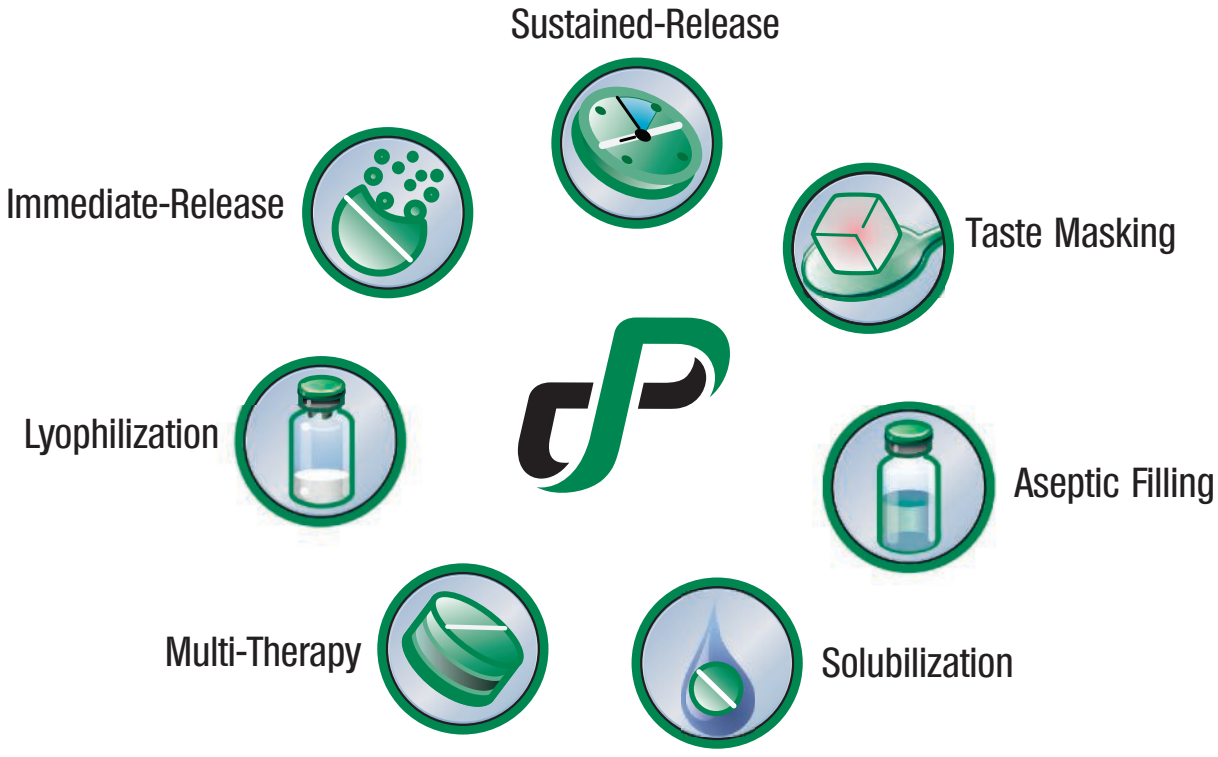

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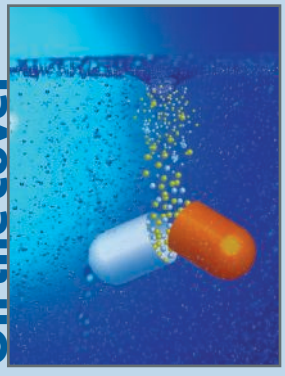
On the cover



Cover story

40 Tackling Solubility Challenges

Patricia Van Arnum

Nanosupensions are among the ways formulation scientists seek to address the problem of solubility.

Capsule Illustration by Dan Ward
Images: Datacraft Co Ltd/Getty images

Features

SPECIAL REPORT

46 Platform Technologies

Moderated by Erik Greb and Angie Drakulich

The standardization of upstream and downstream bioprocessing is growing, but several kinks need to be ironed out.

PHARMA INGREDIENTS

52 Securing the Pharma Supply Chain

Patricia Van Arnum

Regulatory bodies, standard-setting organizations, and industry seek to tackle the problem of counterfeit drugs.

PLUS: Formulation Development Forum.

GENOTOXIC IMPURITIES

74 Genotoxic Impurities

Moderated by Angie Drakulich

Amgen's Bo Shen discusses key challenges to identifying and controlling genotoxic impurities.

Peer-reviewed research

IMPURITIES

58 Evaluating Impurities in Drugs (Part II of III)

Kashyap R. Wadekar, Mitali Bhalme, S. Srinivasa Rao, K. Vigneshwar Reddy, L. Sampath Kumar, E. Balasubrahmanyam, and Ponnaiah Ravi

The authors examine impurities from chiral molecules, polymorphic contaminants, and genotoxic impurities.

Departments/Products

Continued on page 8

On PharmTech.com

Podcast

DCAT President Joan Connolly discusses the association's goals and activities.

Reader comment

"Pharmaceutical manufacturing has been considered a cost center and easy place to cut costs to improve the bottom line," in response to the blog post, "Is the US Facing a Pharmaceutical Manufacturing Gap?" Be part of the discussion at **blog.PharmTech.com**.

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Supplement

Be sure to check out this month's **Solid Dosage and Excipients** special issue, featuring articles on tastemasking, continuous processing, excipient GMP, and more.

Continued from page 6

Columns

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FDA Guides the Way to Biosimilars in the US

Angie Drakulich

Has the long-awaited guidance answered all of the industry's questions?

Almost two years to the date after President Obama signed the Affordable Care Act, introducing a regulatory pathway for biosimilar approval in the United States, FDA has released draft guidance for industry about how to get such a product into the marketplace.

Industry has been at a pivotal standstill since the Biologics Price Competition and Innovation Act (BPCI Act) was passed in 2010, as part of the government's overall healthcare act, but biologics developers and manufacturers seem ready to pounce. According to a press briefing given by FDA's Rachel Sherman in early February, there have been 35 pre-investigational new drug (IND) meeting requests for proposed biosimilars to 11 reference products, 21 pre-IND sponsor meetings held, and 9 INDs received. Sherman is the associate director for Medical Policy within FDA's Center for Drug Evaluation and Research. With the doors to FDA's biosimilar review desk widened, those numbers are likely to skyrocket in the coming months.

The draft guidance—three documents to be exact—includes *Scientific Considerations in Demonstrating Biosimilarity to a Reference Product*; *Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product*; and *Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009.* FDA seems to have gone out of its way to anticipate and respond to key concerns in the documents, the first being whether animal and clinical data from a non-US licensed comparator drug can be used to demonstrate biosimilarity. The answer is yes, according to the *Scientific* draft guidance, although justification and adequate bridging data to a US-licensed reference product will be required in these cases.

Another question addressed is which studies a sponsor needs to perform and submit as part of its 351(k) application—the route to be taken for biosimilar approval. The BPCI Act set the stage for these requirements, and the draft *Scientific* guidance states that companies must include "analytical studies that demonstrate that the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components; animal studies (including the assessment of toxicity); and a clinical study or studies (including the assessment of immunogenicity and pharmacokinetics or pharmacodynamics) that are sufficient to demonstrate safety, purity, and potency in one or more appropriate conditions of use for which the reference product is licensed and intended to be used and for which licensure is sought for the biological product."

Other items provided in the guidance documents are clear definitions for "protein" and "chemically synthesized polypeptides." These definitions are crucial because the pathway legislation added "protein" to the definition of a biological product for the first time.

Also noted are pediatric assessments, which the draft guidance states are required for a biosimilar product that is not deemed "interchangeable." Pediatric study plans should therefore be part of IND applications.

Overall, FDA is focusing on a step-wise approach for manufacturers and a "totality-of-the-evidence" approach for regulatory assessment for biosimilars. Essentially, the manufacturer needs to look at each step of biosimilarity demonstration, starting with extensive structural and functional characterization of both the proposed product and the reference product, to evaluate "the extent to which there is residual uncertainty about the biosimilarity of the proposed product" and then "identify next steps to try to address that uncertainty." For FDA's part, the agency will be reviewing the "totality of data and information submitted in the application…."

Looking ahead, Sherman noted during the February press briefing that FDA still plans to address naming and tracking standards for biosimilars as well as additional exclusivity issues, which are addressed only briefly in the *Q&A* draft guidance.

Also on the docket for the future: standards for "interchangeability." Once a product is proved to be biosimilar, a sponsor can work to demonstrate interchangeability, meaning that the biosimilar product produces the same clinical result as the reference product in any given patient, explained Sherman.

Public comments on the draft guidance documents are due to FDA through the *Federal Register* and will be used to shape the final guidance—hopefully sooner rather than later. The European Union has been ahead of the US in the biosimilar game for years, with approximately 14 approved products under its regional belt. It will be interesting to watch how the global market reacts to FDA's long-anticipated movement forward in this area. **PT**

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

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FDA Encourages Whistleblowers, Just Not Its Own

Amy Ritter

FDA's treatment of whistleblowers lacks internal consistency.

AUGUST STEIN/PHOTODISC/GETTY IMAGES

As part of Ranbaxy's recently announced consent decree, the company is required to set up a program whereby whistleblowers can come forward with information related to potential violations of the Food, Drug, and Cosmetic Act. According to the decree, Ranbaxy must, within 75 days, establish a phone line and a system to receive and maintain submissions from individuals wishing to report suspected violations. The submissions are required to be confidential, there should be no retaliation, and a good-faith effort must be made to investigate any allegations.

But what's good for Ranbaxy has been causing some discomfort for FDA.Whistleblowers from FDA's Center for Devices and Radiological Health have sued the agency over allegedly being harassed and dismissed after publicly questioning the agency's approval methods for devices. The suit brought by the whistleblowers alleges, among other things, that FDA improperly read private emails to support a case for dismissing the plaintiffs. This prompted a letter to FDA commissioner Margaret A. Hamburg from Senator Charles Grassley (R–IA), in which he castigates the agency for perceived mistreatment of the whistleblowers, and includes a series of questions for the agency to answer to clarify its actions with respect to email monitoring.

Among the questions to the agency, Grassley asks, "What steps have you taken to reassure employees that they have a right to direct communications with Congress?" The answer to that question is an important one. FDA should expect no less from itself with respect to whistleblower protection than it demands of others.

Amy Ritter is a scientific editor of *Pharmaceutical Technology*.

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In a world where product recalls can mean the end of a company, all batches must be perfect.

Glassy eyed

"You'd think we would learn," groused our GMP Agent-In-Place. "We've had frequent issues with glass defects in our filled parenteral products, which have included significant Form 483 observations over the years. One batch of a large parenteral product filled into glass vials failed our final visual inspection for cracks. The resulting investigation included an evaluation of the entire glass handling and filling sequence. We found that forklift drivers carrying the incoming glass were not as careful as they could have been in setting down the pallets, and the loading device for sterilizing the dry-heat tunnel was banging the glass into place. These problems were corrected. However, since we've had glass-defect concerns for so long, it was disappointing to see we had missed these. What else might we have missed?"

Blistering problem

"Like many pharmaceutical manufacturers, we purchase medical devices to package with our products to form an administration kit," our GMP Agent-In-Place began. "One such device was a reconstitution spike that is used by the customer to add water to our freeze-dried sterile product. The device was blister-packaged and sterilized. On one occasion, a quality check showed pinholes in the blister, and thus the sterility of the device could not be assured. We identified the source of the problem: the ribbon pins for the dot-matrix printer used to print the lot number on the blister were hitting the blister directly, causing holes. Unfortunately, the product was part of a much bigger lot that was already in distribution. We ended up doing a field correction and sending customers a sterile device, requesting that they reject the devices sent in the package."

The intermediate product was blue, but it was supposed to be white.

I don't recall

"If you watch the recall news carefully, you will see that alcohol swabs have been recalled a couple of times in the past 20 years for nonsterility," noted our GMP Agent-In-Place. "The first time it happened, we knew our company was affected because the problem involved our direct supplier. The second time, we thought we were safe. Unfortunately, we sold a product made by a third party that included the recalled swab. Although FDA didn't request the product be returned, we still had to inform our customers of this issue across 13 countries and 500 affected batches. Ouch."

Lab-house blues

"The intermediate product was blue, but it was supposed to be white," exclaimed our GMP Agent-In-Place. "After questioning the employees, one admitted to losing a ball-point pen in the batch, and the process extracted it with the active material. Our investigation was impressive, especially with regard to the comprehensive testing performed and the detailed safety assessment. Although we could remove the blue color with normal downstream processing, there was no way to assure that all chemical components of the ink would be removed. We processed the intermediate material into a set of vials for use as laboratory in-house controls. The controls were needed in any case. I wasn't happy with the proposed corrective and preventative action, which was a 'Be careful using pens' admonishment for the employees. In the end, we sewed shut the breast pockets of the operators uniforms to reduce the likelihood of a repeat." **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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In the Field

Report from: Brazil

Hellen Berger

Brazil's generic-drug market is growing steadily.

In the past decade, a few million Brazilians out of the country's 200-million population have stepped out of poverty due to the growing economic stability. During the same period, the government allowed generic drugs to enter the domestic market, including through public-health systems, and streamlined regulatory registration of generic drugs. *contin. on page 18*

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contin. from page 16

Similar to many markets, generic drugs in Brazil are produced and sold for an average of 50% less than brand-name drugs. These lower prices, along with the opening of the market, have greatly boosted the generic-drug sector in Brazil, with an average annual growth rate of 30% over the past 10 years, according to Odnir Finotti, executive president of the Brazilian Generic Drugs Industry Association, Pró Genéricos, based in São Paulo.

With innovator-drug patents increasingly reaching expiry, additional generic products have entered the Brazilian market in the past two years. These include generic versions of atorvastatin, rosuvastatin, sildenafil, quetiapin, and valsartan, which now represent around 15% of the sector's income, according to Pró Genéricos. These popular generic drugs are used to treat illnesses such as high cholesterol, erectile dysfunction, pulmonary arterial hypertension, bipolar disorders, high blood pressure, and congestive heart failure.

As a result, the country's generic-drug market grew by 32.2% in terms of sales volume between 2010 and 2011 alone, reaching R$8.7 billion (approximately US $5.05 billion), according Pró Genéricos. The country sold 581 million units of generic drugs in 2011 compared with 439 million units sold the previous year.

Additional innovator patents are expected to expire by 2017, including Pfizer's antipsychotic drug ziprasidone and sirolim, an immunosuppressive drug produced by Wyeth used in organ transplants.

Brazil's generic-drug market grew by 32.2% in terms of sales volume between 2010 and 2011 alone, reaching R$8.7 billion (approximately US $5.05 billion).

Comparative growth

According to Pró Genericos' industry data, most generic-drug markets around the world have reached around 60% of the market share in terms of units sold. In the US, that share is approximately 74%.

"If we add total domestic sales of generics plus the sales of biosimilar drugs, [these products] would hold around 60% of the country's market share in terms of units sold," says Finotti.

In Brazil, "biosimilar" drugs are those sold under the brand name for which the drug's patent has expired, but which have not had bioequivalence tests done. Such drugs in the country are not considered interchangeable and therefore are not labeled as generics.

Pró Genericos' expects generic-drug sales alone to reach 35% of the domestic market share in terms of units by 2015. According to IMS Health, the generic-drug market in Brazil has reached 20.5% of share in financial terms considering the sector's income in Reais.

"We still have a long way to go before considering our generic drug market consolidated," adds Finotti. "We are just starting."

To gain market strength, larger domestic or global pharmaceutical companies, most installed in Brazil, have been eying smaller generic-drug laboratories for acquisitions and to promote mergers. At the same time, they have had to reduce costs in areas such as research, management, and sales, says a pharma analyst and economist.

According to the analyst, brand-name drugs have lost market share to generic drugs in the last years, forcing larger laboratories to cut costs and find alternatives as their margins drop.

Future opportunities lie in generic versions of non-controlled drugs as well as medications that treat coughs and colds, says the São Paulo-based analyst.

Hellen Berger is a freelance writer based in São Paulo.

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Zone in on: Food and Drug Administration Budget

White House Fiscal Year 2013 Budget Includes Increases for the Agency

Susan Haigney

President Barack Obama released his budget proposal for fiscal year 2013. Included in the proposed budget is a $654-million increase in FDA funding, for a total FDA budget request of $4.49 billion. The proposed budget also includes $1.97 billion in user fees, including $583 million in proposed new user fees. The budget request includes "inflationary increases for FDA user fee programs, as authorized by law."

"The resources in this budget will allow FDA to perform its fundamental public health responsibilities in new and more efficient ways. Our budget also supports industry efforts to innovate and bring new products to market that will benefit American patients and consumers and strengthen our economy," states FDA Commissioner Margaret A. Hamburg, in the FDA portion of the proposed budget.

Included in the proposed FDA budget is an additional $363 million earmarked for projects that protect patients, including addressing and detecting risks from products manufactured in China. "The budget contains new resources to increase FDA's capacity to detect and address risks in products and ingredients manufactured in China before they result in harm to Americans," states Hamburg.

The proposed FY 2013 budget sustains the current level of staffing and activities for the Medical Countermeasures Initiative, which is designed to meet national security and public health requirements for medical countermeasures (MCM) readiness. FDA will continue to partner with industry and academia to shorten MCM development timelines and improve success rates.

"The resources in this budget will allow FDA to perform its fundamental public health responsibilities in new and more efficient ways,"—FDA's Margaret A. Hamburg

US Health and Human Services Deputy Secretary Bill Corr, in a press statement, states the proposed Health and Human Services budget "continues to support President Obama's historic push to stamp out waste, fraud, and abuse in our health care system…and our budget helps reduce the deficit by $366 billion over 10 years, almost all of which comes from reforms to Medicare and Medicaid."

The Pharmaceutical Research and Manufacturers of America (PhRMA) expressed concerns about the President's proposed budget and the changes to Medicare in a prepared statement, "Medicare Part D is working well for seniors. Due to competition, costs continue to be far below initial projections. We should not disrupt this successful program."

PhRMA also responded to the budget's handling of data protection, biosimilars, and patents: "We are also troubled by the President's proposal to reduce data protection for innovative biologic medicines, which is critically important to the development of cutting-edge medicines so needed by patients… The biosimilars provision of the health care reform law—the only provision in the law to garner strong bipartisan support—achieves an essential balance. It provides appropriate incentives to support future medical advances. It supports high-value jobs that are critical to our nation's economic recovery. And, it provides savings by creating the first pathway for federal regulators to approve biosimilars.

"Similarly, patent settlements are a vital aspect of a patent owner's ability to protect intellectual property. Restricting such settlements, which already are subject to review by the Federal Trade Commission and the Department of Justice, could discourage pro-consumer settlements, which often bring generics to market years before patent expiration. Without settlements, costly litigation could keep these generics from being available to patients for years," stated PhRMA.

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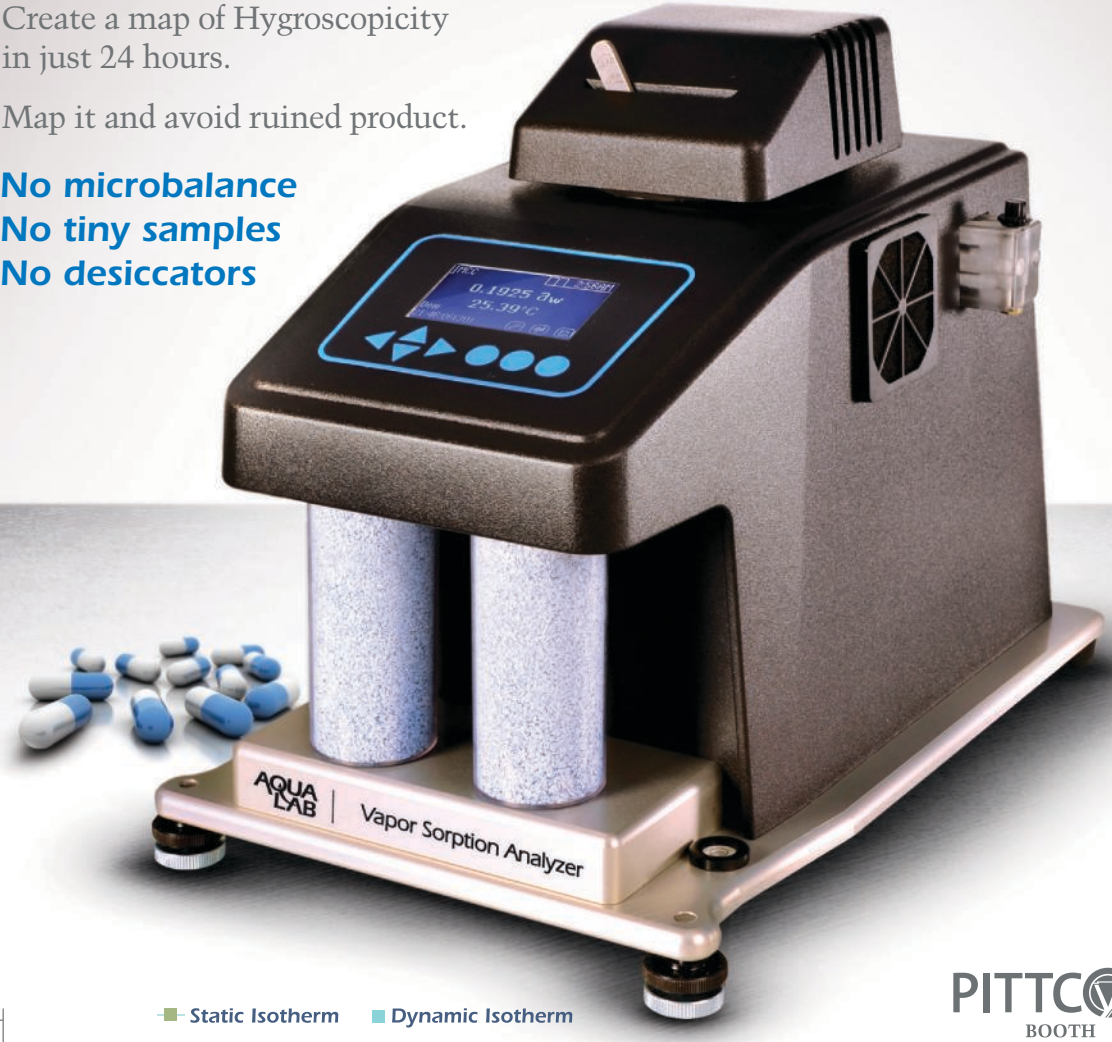

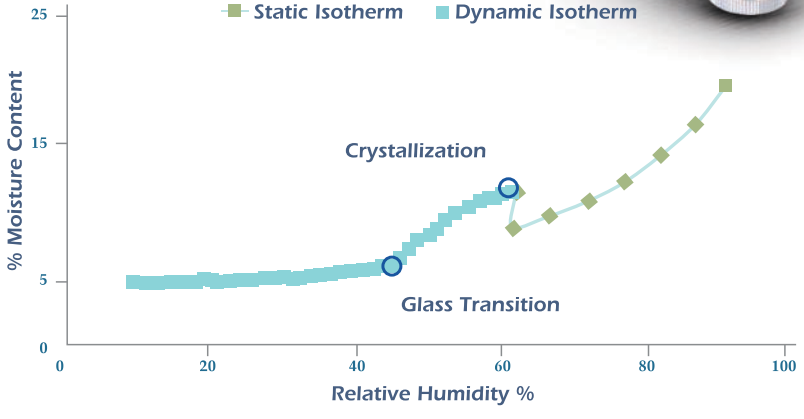

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Consent Decree Filed Against Ranbaxy

Patricia Van Arnum

The US Department of Justice, on behalf of FDA, filed a consent decree of permanent injunction against the generic-drug manufacturer Ranbaxy in the US District Court of Maryland.

The consent decree was filed against Ranbaxy Laboratories Ltd., an Indian corporation, and its subsidiary Ranbaxy Inc., headquartered in Princeton, New Jersey. The decree was filed on Jan. 25, 2012, and is subject to court approval.

In addition to the companies, Dale Adkisson, senior vice-president and head of global quality, and Arun Sawhney, CEO and managing director, both of Ranbaxy Laboratories, and Venkatachalam Krishnan, regional director Americas of Ranbaxy Inc., were named as defendants. The consent decree addresses outstanding cGMP and data-integrity issues at Ranbaxy's Paonta Sahib, Batamandi, and Dewas, India, facilities as well as cGMP issues at Ranbaxy Inc.'s wholly owned subsidiary Ohm Laboratories facility located in Gloversville, New York.

Ranbaxy's Paonta Sahib, Batamandi, and Dewas, India, facilities have been on FDA import alert since 2008, and Ranbaxy has closed its Gloversville facility, according to a Jan. 25, 2012, FDA press release. The consent decree requires that Ranbaxy comply with detailed data-integrity provisions before FDA will resume reviewing drug applications containing data or other information from the Paonta Sahib, Batamandi, and Dewas facilities. Specifically, Ranbaxy must: hire a third-party expert to conduct a thorough internal review at the facilities and audit applications containing data from the affected facilities; implement procedures and controls sufficient to ensure data integrity in the company's drug applications; and withdraw any applications found to contain untrue statements of material fact and/or a pattern or practice of data irregularities that could affect approval of the application.

In addition, the consent decree prevents Ranbaxy from manufacturing drugs for introduction to the US market and for the President's Emergency Plan for AIDS Relief Program at the Paonta Sahib, Batamandi, Dewas, and Gloversville facilities until drugs can be manufactured at such facilities in compliance with US manufacturing quality standards. Once Ranbaxy has achieved compliance with the data- integrity requirements, a third-party expert must conduct audits of the facilities to confirm that compliance is being maintained. The company must authorize an individual to be responsible for all quality-assurance and quality-control activities and establish an Office of Data Reliability.

GlaxoSmithKline Tracks R&D Performance

Amy Ritter

GlaxoSmithKline (GSK) released its fourth quarter and full-year 2011 earnings report on Feb. 7, 2012. In the report, the company tracks its R&D performance, and calculated the return on R&D to be 12%, up from 11% in 2010, and closing in on the company's goal of a 14% return.

In 2008, GSK reorganized its basic research effort to make it more focused and more competitive, mimicking the environment in the biotechnology industry. At that time, GSK created Discovery Performance Units (DPUs) within its Centers of Excellence for Drug Discovery. These units are small, comprising between 5–70 scientists, with each group focusing on one particular disease or pathway. Funding for the groups is competitive, with reviews every three years by a panel containing senior GSK R&D leaders and individuals from outside of the company operating in venture-capital, biotechnology, or pharmaceutical investment. The panel allocates funding according to assessments of potential returns on investment, scientific quality, and opportunity.

This year marks the first of the three-year review cycles for the DPUs. According to the earnings report, four new DPUs have been created and three have been closed. Of the remaining DPUs, six have received increased investment, and five have had investment decreased. Information about exactly which DPUs were affected was not included in the report. More information on the DPUs will be provided in an in-depth meeting for investors and analysts on Mar. 29, 2012.

CSR and sustainability forum

Pharmaceutical Technology's Sourcing and Management eNewsletter provides specialized coverage of the bio/pharmaceutical industry's activities in corporate social responsibility (CSR) and sustainability as well as developments from other business sectors, government organizations, professional, trade, and scientific associations, and NGOs. In the March issue (available at www.PharmTech.com/PTSM):

- Pharmaceutical industry participation in tackling neglected tropical diseases
- A roundup of CSR and sustainability news.

We welcome your ideas to learn about the work of your company or organization in CSR and sustainability. Contact Patricia Van Arnum, executive editor, at pvanarnum@advanstar.com.

Worth Attending

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May 21-23, San Diego, CA
ww.aaps.org

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FDA Isues Draft Crude Heparin Guidance

Amy Ritter

FDA has released a draft guidance for API manufacturers titled *Heparin for Drug and Medical Device Use: Monitoring Crude Heparin for Quality*. The guidance was issued in response to a 2008 incident in which heparin sourced from China was adulterated with oversulfated chondroitin sulfate (OSCS), causing serious adverse reactions in patients.

The draft guidance is intended to alert manufacturers of APIs, pharmaceutical and medical-device manufacturers of finished products, repackers, and others to the potential risk of crude heparin contamination. In addition, it offers guidance for identifying and responding to adulterated crude heparin. FDA defines crude heparin as an unrefined mixture of heterogeneous polysaccharides, including various impurities isolated from mammalian tissues that requires further purification and processing before clinical use.

According to the guidance, FDA considers the presence of OSCS or any nonporcine origin material, especially ruminant material (unless specifically approved as part of the drug application) in crude heparin, or any other form of heparin, to render that drug adulterated under Section 501 of the Food, Drug and Cosmetics Act (21 92 U.S.C. 351).

The draft guidance contains recommendations for procedures to ensure that crude heparin does not contain OSCS or nonporcine origin material, including: testing and confirming the species of origin of crude heparin in each shipment; testing for OSCS sulfate in each shipment; knowing and identifying the actual manufacturer of crude heparin as well as any repackers or distributors who handle it before receipt and use; employing the controls described in the International Conference on Harmonization Q7 guideline to prevent the use of adulterated heparin, and fully and promptly investigating and resolving any deviations in quality; and rejecting and properly disposing of any adulterated crude heparin, as well as notifying FDA of the finding.

Comments and suggestions regarding this draft document should be submitted within 60 days of its publication in the *Federal Register*.

PharmTech Poll: Which injection technology is gaining the most ground in the market?

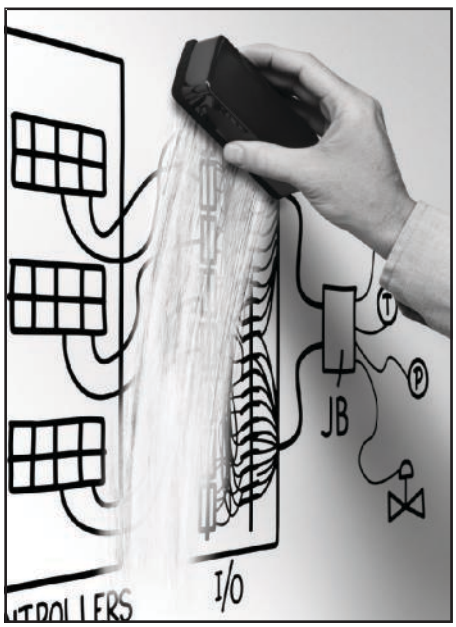
28% Disposable autoinjectors

13% Reusable injectors with replaceable cartridges

11% Retractable safety syringes

49% Needle-free devices

View more online poll s at PharmTech.com/polls.



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Editors' Picks of Pharmaceutical Science & Technology Innovations

Running a manufacturing process efficiently and cost-effectively is an ongoing management challenge. This month's products can help drugmakers save costs in energy, maintenance, and operation. Power monitors from Rockwell Automation show equipment energy consumption. A database and audit program from Endress+Hauser helps manage process instrumentation maintenance. A software tool from Emerson improves start-up and troubleshooting of flow and density meters.

Power monitors provide insight into energy use

Two new Allen-Bradley power monitors from Rockwell Automation give manufacturers more data on how, when, and where energy is used in the production process. Although previous technology covered facility and process-level monitoring, the new monitors allow users to go beyond the process level and collect data from specific, energy-intensive applications.

Rockwell's new wireless PowerMonitor W250 uses a self-generating wireless communications platform that is useful for applications such as ceilings or conveyor belts where hard-wired networking is cost-prohibitive. The wireless network transmits data to the Rockwell Software RSEnergyMetrix software.

The new PowerMonitor 500, designed for smaller consumption applications, has an on-device LCD display so that operators can access real-time energy demand and consumption data at the machine or process level. The monitor has Modbus TCP and EtherNet/IP communication options and is also integrated with the RSEnergyMetrix software.

PowerMonitor 500
Rockwell Automation
www.rockwellautomation.com

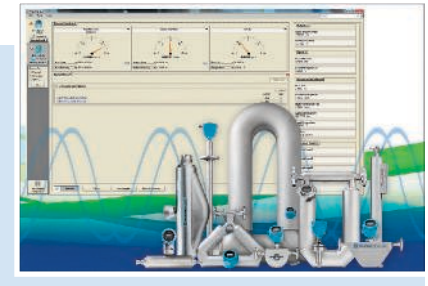
Installed Base Audit Program
Endress+Hauser
www.us.endress.com/services-iba

Program improves maintenance of process instrumentation

Endress+Hauser introduced an Installed Base Audit program to improve management of process instrumentation. Endress+Hauser works with plant maintenance personnel to input process measurement device information into a W@M Life Cycle Management database, and recommends preventive and corrective maintenance of devices. The database enhances traceability and management of all installed measurement devices. For example, the database helps users make sure replacement parts are available for each critical device, but eliminate unnecessary spare parts to reduce stock. Users can also access measurement device documentation through the database. Software tools allow users to control and document maintenance and calibration work.

Software tool helps configure and troubleshoot flow and density meters

Emerson Process Management's Micro Motion ProLink III, a Microsoft Windows-based tool for Micro Motion Coriolis flow and density meters, provides an intuitive interface for users. A guided connection wizard, simulated device feature, and offline configuration tool aid set-up. For troubleshooting, a single, full diagnostics display shows process variables and alerts, and categorizes alerts by severity. The software can simultaneously connect to multiple devices, allowing the user to view and change process conditions across more than one transmitter at a time.



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Communications Advances Present Manufacturer Challenges

NIKOLAI PUNIN/GETTY IMAGES

Jill Wechsler

Social-media use raises questions about applying old standards to new information technology.

Much of the world now uses the Internet to communicate with friends and relatives, to market goods and services, and to convey information on important developments around the globe, including health and medicine. Healthcare professionals and patients are turning to online disease sites for assistance in diagnosing and treating cases. Twitter and Google Flu Trends help predict epidemics and emergency room traffic. Worldwide use of mobile communications devices further expands two-way communications about healthcare activities and problems.

These developments leave pharmaceutical manufacturers in regulatory limbo due to curbs on what firms can tell the public about their products and operations. Widespread interest in pharmaceutical company research findings, product safety, and marketing and production speaks to the need for industry to use the Internet to disclose information as broadly as possible. Yet, regulations that ban manufacturer discussion of off-label drug uses and require full disclosure of product risks limit what manufacturers can say about approved medicines. Industry, as well as the larger healthcare community, want FDA to clarify how its rules on drug marketing and promotion can fit the age of instant Internet communications and unfettered public access to information previously limited to health professionals. FDA officials have been promising guidance in this area for several years, but little has emerged so far.

Broad concerns

The relationship of pharmaceutical companies to social media communications gained prominence in 2009, when FDA issued Warning Letters admonishing 14 drug and biotech manufacturers for sponsored links on Google and other Internet search engines with information on drug use but without providing adequate risk information. FDA officials said that it is not sufficient to provide a link to more detailed safety information, and that all Internet postings sponsored by manufacturers have to comply with marketing standards for promotional materials. That policy tossed out the assumption that marketers could be in compliance by providing risk information through one click to a relevant source.

FDA acknowledges that the Internet can produce misinformation, but fails to explain how companies should deal with erroneous statements about their products.

FDA held a public hearing on the industry's use of social media in November 2009 to address these issues further. Approximately 50 organizations presented their views, including manufacturers, medical website operators, and Internet search engines. They discussed when and how manufacturers can be held accountable for or able to correct erroneous information in online communications generated by third parties; when it is appropriate to use social media to provide links to non-company healthcare and medication information; how social media can facilitate reporting of adverse drug events; and how companies should submit real-time, online communications to meet requirements for agency review. At the top of the agenda was the Warning Letter issue: namely, how pharmaceutical companies could adhere to policies for drug marketing and communications when it is difficult to fully explain drug risks and benefits in a 140-character Twitter posting.

This public discussion about using online and social media outlets to communicate information about drug products has heightened public use of online resources for relevant medical information, according to a May 2011 analysis by the Pew Research Center. A Pew survey conducted in 2010 found that 24% of Internet users have consulted online reviews of drugs or medical treatments, and 4% have posted personal experiences involving a particular drug. Almost one-quarter of Internet users look for drug safety and recall information online, and the numbers are higher for individuals caring for loved ones and for people with chronic conditions or disabilities.

FDA's Office of Prescription Drug Promotion (OPDP) in the Center for Drug Evaluation and Research (CDER) has been studying concerns and proposals for Internet communications aired at the public meeting and in subsequent public comments with an eye toward providing guidance that will assist industry in

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adapting marketing practices to the Internet. The agency now plans to develop several guidances on "concepts that have long-term applicability," explained Jean-AhKang, assistant to the OPDP director, at CBI's January Pharmaceutical Compliance conference in Washington, DC. Instead of issuing platform-dependent policies that would apply to posting information on, for example, Twitter or YouTube, which might become outdated quickly by changing technology, the agency is looking to address broader Internet communications issues. These issues include messages with space limitations as found in banner ads or social-media listings; manufacturer accountability for online communications; links to Internet websites; correcting misinformation on third-party websites; and how to meet FDA prenotification policies for real-time communications activity.

Limiting off-label information

FDA provided some clues to how it will address industry use of "emerging electronic media" in a draft guidance published in December 2011 on how drug, biotech, and device manufacturers should respond to unsolicited requests for off-label information. The proposal deals with an issue raised in a citizen petition filed with FDA in July 2011 by pharmaceutical manufacturers seeking clarification on several off-label communications topics. The petitioners sought advice on handling off-label information when dealing with unsolicited requests for information, as well as during scientific exchange; when providing information to formulary committees and payers; and in disseminating clinical-practice guidelines prepared by third parties.

This recent guidance from FDA, *Responding to Unsolicited Requests for Off-Label Information About Prescription Drugs and Medical Devices,* mentions social-media communications as part of its larger discussion of off-label communications. The main thrust of the document is to clarify that manufacturers may provide information on off-label drug uses, but only in response to "unsolicited" requests from individuals completely independent of the manufacturer; any hint that the company stimulated the request makes it a solicited request, and potentially violative.

Here is where social media comes in: queries spurred by a company video posted on YouTube, for example, would shift the question into the "solicited" category, which may be violative. Social media sites also are mentioned as possible forums for a company to receive questions from the public, including those involving off-label drug uses.

Probably the most contentious item in the guidance is FDA's proposal that manufacturers handle requests for information made in public or through the Internet in the same way as queries made by email or the phone: provide a response only to the individual requester in "a private, one-on-one communication" and not communicate it online. The agency's concern is that a public response exposes those not mak-

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ing the query to off-label information, and that such information could remain on a website after it becomes outdated. When receiving an unsolicited request on an issue related to off-label use, FDA advises manufacturers to provide contact information to medical or scientific personnel (not salesmen) and direct the individual to follow up off-line. Such information should be truthful, balanced, nonmisleading and reflect an effort by the company to avoid promoting off-label drug uses. This means, however, that a broad audience can see a query and any erroneous, independent statements it generates, but not the company's answer.

Although the guidance disappointed those anticipating more specific advice on social-media communications, the document is important because it includes new Internet technologies as part of the discussion on a critical off-label communications topic, says Peter Pitts, president of the Center for Medicine in the Public Interest. Pitts notes that FDA acknowledges that Internet sites can produce a good deal of misinformation, but the agency fails to explain how companies should deal with erroneous statements about their products, in all media.

More thorny issues

These limits on Internet and social-media communications raises concerns about broader curbs on industry use of modern communications technology for a broad range of corporate and operational functions, such as reporting corporate news and developments, recruiting patients for clinical trials, or operating hotlines to receive consumer questions and comments.

Social media appears to have great potential for expanding public reporting of adverse drug events, for example. FDA posts online forms for collecting adverse events under its MedWatch program, but the form is long, detailed, and not widely used. Because consumers already turn to social media to discuss experiences with drugs and biotech therapies, as noted in the Pew study, there's interest in imbedding an adverse event reporting "widget" into social media sites to encourage wider public reporting of drug use problems.

Manufacturers are leery of such initiatives, because they would have to scour Twitter and Facebook and other sites to identify such reports and respond to them, which could be a monumental task. Even with a common format, many publicly reported adverse events would be useless if they fail to clearly identify the patient, reporter, dosage, and type of event. Furthermore, as noted above, a pharmaceutical company still would be constrained in addressing misleading adverse-event reports, especially those involving off-label use.

FDA has a Facebook page and uses Twitter to discuss product approvals. Regulators and manufacturers use blogs and social media to alert the public to recalls and safety issues. As these activities expand, industry needs a way to ensure the accuracy of information posted online about company operations and products, and to correct misleading or fraudulent postings. **PT**

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Hot-Topic Roundup

User Fees

Hearings last month before the US House Energy & Commerce health subcommittee provided FDA officials, industry representatives, and the healthcare community an opportunity to comment on proposals for updating the Prescription Drug User Fee Act (PDUFA V). There was general support for stronger FDA oversight of the global drug supply chain, including stiffer import controls and more inspections of foreign manufacturers. More contentious is whether to loosen conflict-of-interest requirements for advisory committee members that Republicans say are too stringent and can delay new drug approvals. There was debate over proposed changes to policies that offer incentives for manufacturers to study the safety and efficacy of drugs for children. Complaints about the proliferation of Risk Evaluation and Mitigation Strategies (REMS) may be off the table, however, due to FDA efforts to scale back that program. More hearings are expected in the Senate, as Congress strives to complete work on user fees for drugs, generic drugs, biosimilars and medical devices by summer.

Unapproved drug violations and claims

The era of Big Pharma fraud cases involving promotion of unapproved drug uses may be passing, according to leading state and federal enforcement officials. Prosecutors are shifting their focus to criminal actions involving drug manufacturing and quality, as well as promotion of economic superiority and misrepresentation of research results. "We anticipate the look of our cases will be changing–and for the better," predicted Sara Bloom, assistant US attorney for the District of Massachusetts, noting at the January 2012 pharma compliance conference sponsored by CBI that "the days of rampant kickbacks to physicians and luxury golf outings are over."

Instead, Bloom and others have their eyes on marketing claims about drugs saving money or being superior to a generic product, but without supporting clinical data. She also expects more actions involving violative drug manufacturing practices and shipments of adulterated products. John Krayniak, assistant attorney general in New Jersey, noted increased interest in long-term care of the elderly, including misuse of drugs such as antipsychotics in nursing homes.

FDA's Sentinel system

FDA's Sentinel Initiative is moving towards full implementation of a system that will assess pre- and postapproval drug use based on health information from on more than 100 million individuals. The system now enables FDA to evaluate data from 17 healthcare systems to detect and evaluate signals of safety problems for approved drugs. Over the past three years, the pilot "mini-Sentinel" system has responded to queries, for example, about whether lipids cause heart attacks and links between angiotensin receptor blockers and celiac disease. The ability to review millions of cases has helped evaluate concerns about rotavirus vaccines causing intussusception and if patients experiencing venous thromboembolism due to the HPV4 vaccine.

Eventually, the system will generate evidence to support more appropriate uses of medicines and will help conduct requested post-approval and outcomes studies. FDA and manufacturers may be able to evaluate fairly quickly potential risks associated with new drugs to gain added assurance of safety, or to support labeling changes. The system is moving beyond drugs to also assess blood and blood-derived product use and to link up to state immunization registries to expand oversight of vaccine safety. FDA further anticipates being able to evaluate the impact of labeling changes on health outcomes. *contin. p. 36*

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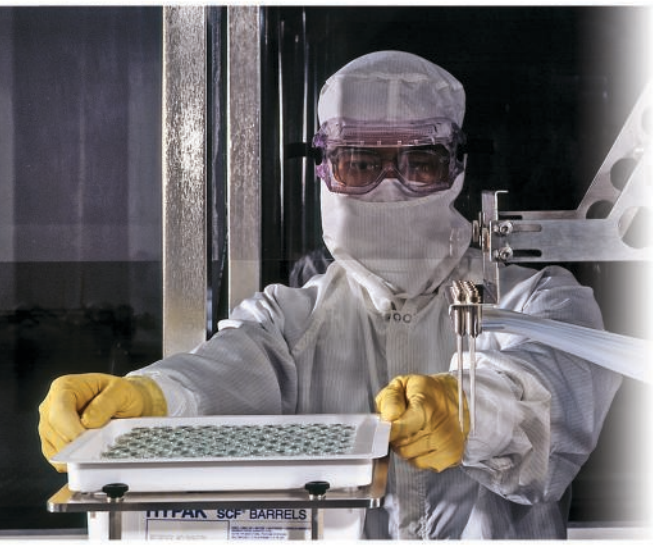

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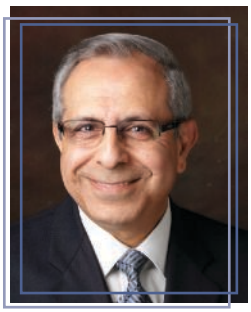

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Comparative effectiveness

The Patient-Centered Outcomes Research Institute (PCORI) is setting priorities for how it will spend some $2 billion over the next 10 years to help determine effective medical treatments, and drug manufacturers are watching its decisions very closely. PCORI issued a draft priorities and research agenda in January, as required by the Affordable Care Act (ACA), but that only laid out five broad categories of interest, and avoided specifying individual research topics. The most important priority area is to assess prevention, diagnosis and treatment options, with an eye to identifying those products and practices that produce superior patient outcomes. The Institute also will devote its resources to improving healthcare systems, accelerating methodological research, reducing health disparities and identifying ways to improve patient compliance through better communication and dissemination of recommended practices.

Cost is not supposed to a research factor, but PCORI can consider the impact of a medical practice on national health expenditures. That fuels concerns among pharma companies that such studies will lead to recommendations unfavorable to new, more expensive technology. PCORI officials are making an extensive effort to seek broad public input on its program to hear public comments on its proposed agenda. PCORI plans to award 40 grants this year, with initial grants announced in May and another round in December.

Meanwhile, the National Pharmaceutical Council, which is spearheading pharma action on comparative effectiveness research (CER), announced funding for five projects that deal with varying patient responses to treatment. The research will assess the impact of CER on health policy decisions, the role of patient heterogeneity in response to treatment, and how CER affects treatment decisions by managed care pharmacy and medical directors.

Drug supply

Efforts to strengthen the Strategic National Stockpile (SNS) of medical products needed for health emergencies is prompting regulatory and policy changes. In February, FDA issued a final rule designed to make it easier to keep an experimental drug or biologic in the stockpile and not have to discard it when it was formally approved and revises its label. In addition, the Biomedical Advanced Research and Development Authority (BARDA) in the US Department of Health and Human Services (HHS) is taking a number of steps to boost development of medical countermeasures for the stockpile program. BARDA is looking to modify product expiration requirements to extend the shelf life of stockpiled products, explained BARDA principle deputy director Carol Linden at the Phacilitate vaccine forum in Washington in January. There also is interest in stockpiling manufacturing intermediates, such as frozen bulk products, and in funding R&D on multiuse products such as broad-spectrum antimicrobials, on radiation countermeasures, and on new diagnostics for all agents.

Recently issued key guidance documents

- Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009 (FDA, Draft)
- Scientific Considerations in Demonstrating Biosimilarity to a Reference Product (FDA, Draft)
- Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product (FDA, Draft).
- Heparin for Drug and Medical Device Use: Monitoring Crude Heparin for Quality (FDA, Draft).

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Defining Conflict of Interest

Christopher Milne

The divide between innovation and conflict of interest in medical research is not so clear.

What is a conflict of interest? Gilbert's Law Dictionary says that a conflict of interest (COI) arises when private interests clash with one's duty to serve the public interest. *Prejudicial interest* refers to having an interest in a topic that may affect one's ability to fairly and objectively consider the subject. *Equipoise* is a scientific concept by which a researcher believes in a hypothesis, yet no factual proof yet exists. Equipoise becomes conflict when medical professionals convince themselves they are right despite evidence to the contrary because of their own self-interests. When that happens, an ethical line in the sand is crossed. It can be hard to tell when that line gets crossed, no matter how rigorously a decision, affiliation, or financial arrangement is examined.

There are a panoply of new standards, rules, and guidelines relating to COI for medical research. The Physician Payment Sunshine provisions under the *Patient Protection and Affordable Care Act* mandate medical product and device companies to report any kind of transfer of value to physicians and post it in a public database. A half dozen states, with more likely to follow, have rules governing conduct for pharmaceutical and medical-device manufacturers that require reporting, prohibit, or impose restrictions on a wide array of physician–industry activities ranging from free meals to continuing medical education courses. At the federal level, rules under the National Institutes of Health (NIH) require medical researchers receiving federal grants to disclose any industry payments over $5000 and allow a university's NIH grants to be withdrawn for egregious violations or lack of oversight.

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In the private sector, medical researchers are required by some medical publications to fill out standardized forms that enumerate payments from consulting work, honoraria, expert testimony, grants, commissioned manuscripts, intellectual property rights, royalties, stock holdings, and advisory boards. The American Medical Students Association ranks medical schools annually based on their COI polices, and the Pew Prescription Project and Yale University both have conducted recent surveys of patient attitudes regarding physician ties to pharmaceutical companies.

Why the brouhaha? In part, it is because of the media's attention to this type of story. A recent example reported in *MedPage Today* concerned Thomas Zdeblick, chair of the Department of Orthopedics at the University of Wisconsin–Madison, which according to the article, received more than $25 million in royalties since 2003 from Medtronic, a firm that sells spinal devices. Reportedly, this funding occurred while the hospital affiliated with the university spent $27 million on Medtronic spinal products from 2004–2010. Zdeblick also received more than $1 million in compensation from the university in 2010, according to the article (1).

But is this a case of COI? In this particular case, the selection of implant devices was done by a review committee. Moreover, Zbedlick's influence on residents and fellows was mitigated by the fact that they work with multiple surgeons who have differing views and preferences for various devices, and students are told about the royalties Zdeblick receives. The entire management plan, under which he operates, is a shared responsibility of the doctor, the department, and the dean's office.

That brings us full circle to definitions of COI and equipoise. The foundation of medical research is the state of clinical equipoise, which is met when there is genuine uncertainty within the expert medical community—not necessarily on the part of the individual investigator—about the preferred treatment (2). It is a shared responsibility. Implementing a just and workable system of COI monitoring is not something that can be achieved by simply legislating against bad acts. Rather than developing a system that prevents bad acts, legislation often creates a chilling effect—an inhibition or discouragement of legitimate expression, such as innovation.

Curbing innovation is the last thing we can afford in biomedical R&D. The turnover rate of researchers who have not submitted an investigational new drug application since 2006 is 35% (3). While NIH biomedical research funding has flatlined for the last several years, the number of doctors applying for NIH grants has flatlined for the last few decades. The average age of first-time biomedical grantees has risen six years to 42 years old (4).

Cures for cancer and neurodegenerative disease are elusive and costly as are the solutions to the crushing debt of biomedical education. There is a strong need for translational approaches in R&D, creation of interdisciplinary MD–PhD research teams, and cross-fertilization of private and public sector resources. These are conflicts of the public interest and that is where change should focus.

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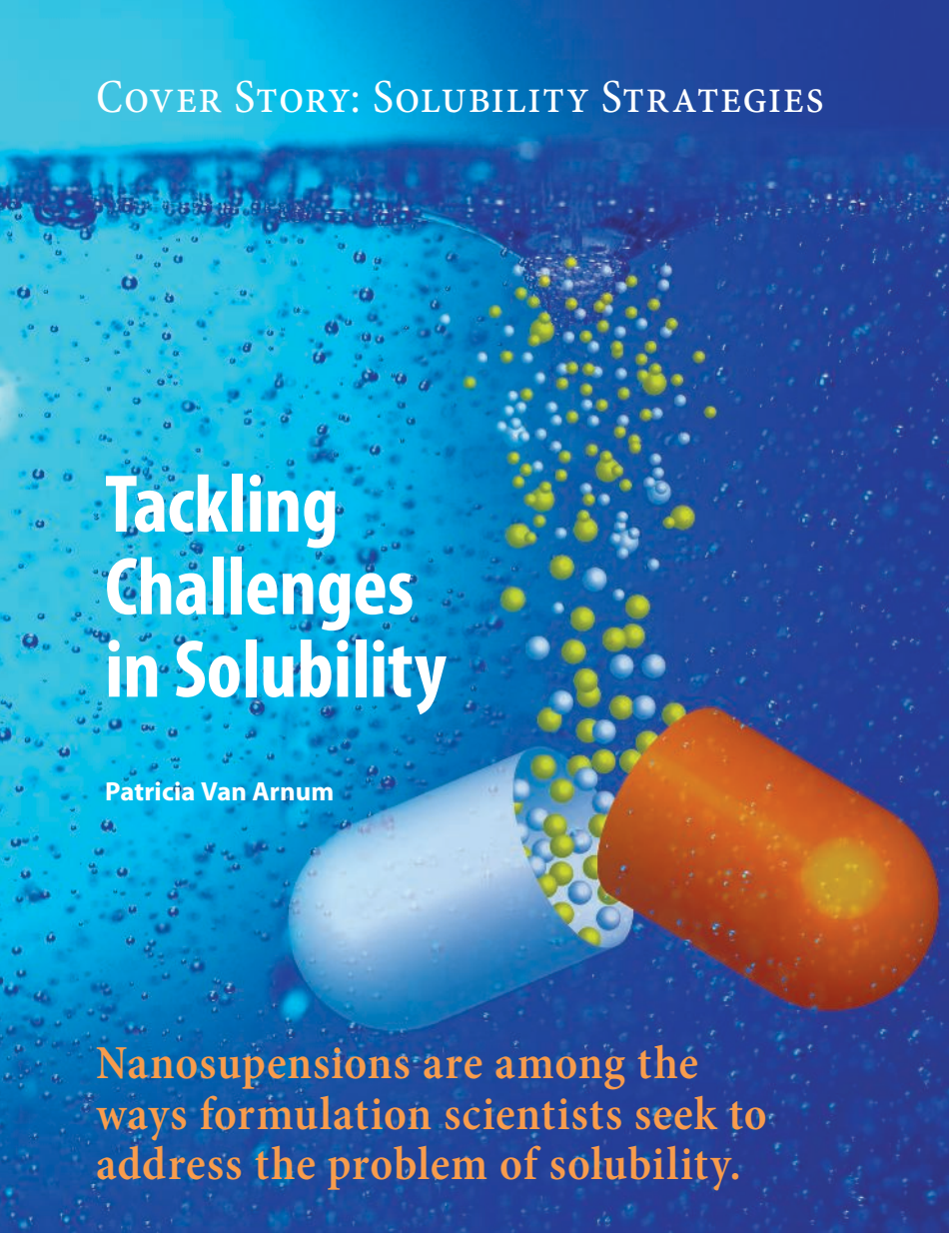

Tackling Challenges in Solubility

Patricia Van Arnum

Nanosupensions are among the ways formulation scientists seek to address the problem of solubility.

Strategies to improve drug solubility are of crucial importance to the pharmaceutical industry. Advancement of high-throughput screening techniques for lead identification in drug discovery has had the benefit of generating more potential drug candidates, but with this increase in the diversity and number of drug molecules comes challenges (1). Most notably, more leads are being identified with high-molecular weights and lipophilicity and thus have poor water-solubility (1). Industry estimates are that as much as 60% of drugs currently in development may be classified as poorly water-soluble (2). Poor solubility is problematic because of the resulting decrease or variability in bioavailability, which affects clinical efficacy and safety, such as through necessitating higher dosing regimens to achieve therapeutic effects (1). Enhancing bioavailability of poorly water-soluble drugs, therefore, has strong clinical and commercial significance.

Classifying poorly soluble drugs

The Biopharmaceutics Classification System (BCS) is a scientific framework for classifying drug substances based on their aqueous solubility and intestinal permeability (2). When combined with the dissolution of the drug product, the BCS takes into account three major factors that govern the rate and extent of drug absorption: dissolution, solubility, and intestinal permeability. According to the BCS, drug substances are classified as follows:

- Class I: high solubility and high permeability
- Class II: low solubility and high permeability
- Class III: high solubility and low permeability
- Class IV: low solubility and low permeability (3).

Various approaches can be used to address problems of solubility, such as particle engineering, salt selection, amorphization of the compound, use of surface-active agents or cosolvents, polymeric stabilizers to achieve supersaturation, and solid dispersions and solutions (2). Physical modifications may occur through such techniques as micronization, nanonization, and sonocrystallization (4). Although micronization of powders can be useful to improve solubility, the resulting particle size of drug powders of between 1 and 10 µm to increase the surface area and the dissolution velocity may be insufficient to overcome bioavailability problems of many poorly soluble BCS Class II drugs (4). Nanonization moves beyond micronization to further reduce particle size as a means to increase dissolution rates and bioavailability of poorly water-soluble drugs (4). Nanozination strategies include increasing the surface area-to volume ratios of drug powders, changing crystalline forms, and developing nanomaterials for drug delivery (5).

Approaches in nanonization

Several drug-delivery companies and specialty pharmaceutical companies have developed technology platforms involving nanozination. Perhaps the most well known and established technology is the NanoCrystal technology of the former Elan Drug Delivery Technology, which was acquired by Alkmeres in 2011 (4). The technology has been manufactured at a commercial scale since 2001, according to company information. NanoCrystal technology involves reducing the size of drug particles, typically to less than 2000 nm. By reducing particle size, the drug's exposed surface area is increased. The nanoparticles are then stabilized to maintain their reduced particle size. The result is a stable drug formulation that shows an increased dissolution rate. Five products have been launched

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using the company's NanoCrystal technology, according to the company (6).

The specialty pharmaceutical company SkyePharma has several technologies in its solubilization toolbox: the IDD (insoluble drug delivery) platform, which coats particles with phospholipids; DissoCubes, which reduces drug particle size to enable rapid absorption; and SLN (solid lipid nanoparticles), which takes advantage of lipid digestion to promote drug absorption by the gastrointestinal tract (4, 7).

DissoCubes are crystalline nanoparticles of active substance obtained by a liquid state high-energy process using a high-pressure piston gap homogenizer to reduce the drug particle size in the presence of surface modifiers that associate at the freshly generated drug interface (4, 8). A particle-size reduction from approximately 50 µm to about 0.5 µm is achieved resulting in a homogenous and stable formulation. The nanosuspensions can be formulated into various dosages forms (8).

The IDD platform consists of three main technologies focused on dispersible narrow particle-size distribution dosage forms derived from surface-modified micrometer to submicrometer-sized particles or droplets stabilized by surface modifiers, specifically phospholipids. The IDD-P (MicroParticle) is a microparticulate variation of the IDD drug-delivery system, which consists of a pure solid drug in the core of the particle. IDD-D formulations (MicroDroplet) involve liquid drug substances (8).

IDD-P and IDD-D formulations are produced by application of high shear, cavitation, or impaction (e.g., attrition, homogenization, microfluidization, milling, ultrasonication) to reduce the drug particle size in the presence of phospholipids (and/or other surface modifiers) that associate at the freshly generated drug surface. A particle-size reduction from approximately 100–200 µm to about 1 µm is achieved resulting in a homogeneous and stable formulation (8).

The company's IDD-D and IDD-P technology apply physical or mechanical processes to achieve the desired particle size. The third technology in SkyePharma's IDD platform, IDD-SE (Self-Emulsifying), involves self-generation of surface-stabilized micrometer- to submicrometer-sized particles or droplets when the dosage form is exposed to an aqueous medium such as those in gastrointestinal or vascular compartments (8).

An example of a commercial drug using SkyePharma's IDD technology platform is Triglide (fenofibrate), an oral treatment for elevated blood lipid disorders, launched in 2005 and marketed in the United States by Shionogi Pharma. Some fenofibrate-based products are insoluble in water, which may result in variable uptake from the stomach and require the patient to take the tablets with food. Triglide, SkyePharma's formulation of fenofibrate, uses the company's IDD platform technology, which has comparable absorption under both fed and fasting conditions. Triglide is manufactured at the company's Lyon, France, manufacturing facility leased by SkyePharma to Aenova (8).

Aptalis Pharma, a specialty pharmaceutical company formed from the merger of Axcan and Eurand in 2011, provides bioavailability-enhancement technology through Aptalis Pharmaceutical Technologies, which includes its Biorise technology. The Biorise technology breaks down the crystalline drug into nanocrystals and/or an amorphous (noncrystalline) drug that is stabilized in a carrier system to maintain the drug in its activated form for the duration of its shelf life (9). This approach creates a greater surface-area-to-volume ratio that increases the intrinsic solubility and dissolution rate of poorly water-soluble drugs, thereby enhancing their rate and extent of absorption. The analgesic megestrol acetate and the nonsteroidial anti-inflammatory drug nimesulide are two examples of drugs using the Biorise technology (9).

Researchers at the Novartis–MIT Center for Continuous Manufacturing, Department of Chemical Engineering, Massachusetts Institute of Technology (MIT), recently reported on the development of nanocrystals in a continuous manufacturing environment. Specifically, they used an electrospray technology followed by annealing at high temperatures to produce nanocrystals of carbamazepine, a poorly water-soluble drug, in a continuous manufacturing process. The researchers reported that the solubility and dissolution rates of carbamazepine nanocrystals increased significantly as compared with carbamazepine bulk particles (10).

Controlled agglomeration

Dispersing a poorly soluble compound in a polymeric matrix to improve solubility and therefore bioavailability is another

On the horizon: carbon nanoparticles in drug delivery

A mixture of current drugs and carbon nanoparticles shows potential to enhance treatment for head-and-neck cancers, according to research by Rice University in Houston and the University of Texas MD Anderson Cancer Center. The therapy uses carbon nanoparticles to encapsulate chemotherapeutic drugs and sequester them until they are delivered to cancer cells.

The new strategy by Rice chemist James Tour and Jeffrey Myers, a professor of head-and-neck surgery at MD Anderson, combines paclitaxel and cetuximab with hydrophilic carbon clusters functionalized with polyethylene glycol, known as PEG-HCC, according to a Feb. 16, 2012, Rice University press release. Cetuximab, the targeting agent, is a humanized monoclonal antibody that binds exclusively to the epidermal growth factor receptor (EGFR), a cell-surface receptor overexpressed by a large percentage of head-and-neck squamous cell cancers. Because paclitaxel is hydrophobic, the substances are generally combined with Cremophor EL, a castor oil-based carrier that allows the compound to be delivered intravenously to patients. The researchers found a simple way to mix paclitaxel and cetuximab with carbon clusters that adsorb the active ingredients. The new compound is water-soluble and is more effective at targeting tumors than when paclitaxel is administered with Cremophor, according to the release.

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strategy. To produce the solid solutions or solid dispersions, various methods can be used, such as hot-melt extrusion, spray-drying, melt congelation, and nanocrystal technology (11, 12). Veloxis Pharmaceuticals (formerly called LifeCycle Pharma), a technology spinoff from the Danish pharmaceutical company H. Lundbeck, uses a proprietary process, MeltDose, based on controlled agglomeration, to address the problem of poorly soluble drugs (12–13).

Controlled agglomeration can be used to address solubility.

Under the MeltDose approach, a low water-soluble drug substance is dissolved in a vehicle system that is optimized for each drug substance. The drug substance is spray-dried on an inert particulate carrier using fluid-bed equipment and solidified when disposed on the carrier. The carrier captures the active drug in a nanocrystalline or microcrystalline state or as an amorphous solid dispersion. This step is followed by agglomeration that is controlled by optimizing temperature and feed rate to produce the granules, which are directly compressed into tablets. Once in tablet form, the dissolution profile and particle size remain stable (12-13).

The selection of the vehicle to match the physiochemical properties of the API is an important consideration in the process. In some formulations, the API will be present as an amorphous solid dispersion, such as in hot-melt extrusion and spray drying, but in other formulations, the API will be present as crystals in nanometer or micrometer size, resembling nanoproducts more (12–13).

MeltDose, the proprietary process that Veloxis Pharmaceuticals has developed, centers on the controlled agglomeration process. The controlled agglomeration process has some similarities to fluid-bed granulation. Controlled agglomeration involves placing solid carrier particles in a conventional fluid bed, unto which a liquefied vehicle containing the API is sprayed. When the liquid vehicle is cooled down on the carrier, it agglomerates and forms granules. The controlled agglomeration process is water-free, and in contrast to conventional fluid-bed granulation, uses liquefied (i.e., melted) polymers as the polymeric vehicle. The polymeric vehicle is melted in a specially designed heated melt unit that controls temperature and pressure of the melted vehicle, which passes from the melt unit to a specially designed spray nozzle in the fluid bed. The produced granules are compressed to tablets using conventional tablet presses (12–13).

The polymer vehicles used in the MeltDose process can include a range of hydrophilic and lipophilic materials and are selected for their solubility-enhancing properties and compatibility with subsequent processing steps. Examples of vehicle systems are solid or semisolid polymers with a melting point between 40 and 80 °C, such as polyethylene glycol 6000, poloxamers, and various types of gelucires. The resulting granule size varies with the choice of excipients and lies typically in the range of 200 to 500 µm. The vehicle temperature, the spray rate, the atomizing air volume, and product temperature all are important process parameters to consider during the controlled agglomeration step. Also, the addition of different surfactants can result in different sizes of API crystals in the granule (12-13).

Fenofibrate, a lipid-regulating agent to control cholesterol and marketed as Fenoglide in the United States, was the first product approved in the US using the MeltDose technology. Veloxis Pharmaceuticals is working on other formulations that use the MeltDose process. The company has developed a once-daily modified-release formulation of tacrolimus, a poorly soluble compound with a water solubility of 4–12 µg/m, and the same API as in Astellas's Prograf, an immunosuppression drug used in kidney and liver transplants. Veloxis Pharmaceuticals has developed an amorphous solid-dispersion formulation of tacrolimus. The API was dissolved in a melted vehicle at elevated temperature. The solution was sprayed onto an inert carrier in a fluid bed. The resulting granulate was blended with a disintegrant and lubricant and compressed into tablets. The modified-release tablet formulation using the MeltDose technology was developed and tested in humans and is currently in late Phase III testing for the prevention of organ rejection with kidney transplants. Veloxis Pharmaceuticals expects to file for regulatory approval for the product, LCP-Tacro, in the US and European Union in the first half of 2013 (12).

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Platform Technologies

Moderated by Erik Greb and Angie Drakulich

The standardization of upstream and downstream bioprocessing is growing, but several kinks need to be ironed out.

Platform technology is becoming a popular industry approach for bioprocessing, but just how are companies using it? *Pharmaceutical Technology* talked to industry experts to gain insight: Morrey Atkinson, PhD, CSO and vice-president of R&D and Drug-Substance Manufacturing at Cook Pharmica; Peter Moesta, PhD, senior vice-president of Biologics Manufacturing and Process Development at Bristol-Myers Squibb; and Jim Powell, business development manager at Ashai Kasei Bioprocess.

PharmTech: How might platform technologies be applied to upstream and downstream processes? Is one easier than the other?

Atkinson (Cook): It is not easier to develop platforms for either upstream or downstream, it is just different. The main difference in developing platform processes for either is that, in most cases, one develops upstream processes for the cell line and the expression system, while downstream processes are tailored to the molecule itself. If the molecules are of a similar type, then the downstream process becomes easy to develop.

In terms of difficulty, the cell lines and expression systems are inherently variable, and clone-to-clone variability adds to the complexity. Scale factors are also more difficult to control in cell culture and fermentation. In general, upstream therefore probably poses a slightly greater challenge, assuming that the molecules are in a given class or category.

Moesta (Bristol-Myers): With today's level of know-how in molecular biology and expression, platform technologies are easier to develop for upstream processes. Identification of a preferred strain or cell line for microbial or mammalian expression, combined with a well-developed expression vector, is the first step in establishing a production platform. This step allows for the use of standardized fermentation or cell-culture conditions requiring limited media and feed optimization. The use of platform expression systems and upstream conditions allow for the generation of significant process experience and forms the basis for developing downstream platforms to the extent possible.

It is easiest to develop a standardized process for initial downstream steps (e.g., centrifugation and depth filtration for cell-culture products). For monoclonal antibodies (mAbs), where the Fc protein domain–Protein A interaction can be exploited to capture the protein from clarified cell-culture broths, additional platform steps are possible (e.g., Protein A-based affinity chromatography and viral inactivation and filtration steps). The final purification steps (i.e., polishing) need to be tailored to the particular antibody at hand and usually require individual optimization. For other proteins, downstream processing becomes less amenable to the platform approach. Individual process steps can be standardized, but will need to be pieced together and optimized on a case-by-case basis.

BMS is developing molecules to which we apply platform-based approaches, including antibodies and adnectins. But even when dealing with well-defined classes of proteins, key challenges for establishing production platforms result from unique properties of individual proteins, such as charge heterogeneity, differences caused by post-translational modifications, and stability. These unique properties can impact both the cell's ability to express a correctly folded and stable protein as well as purification of a homogeneous drug substance.

PharmTech: Could a platform for purification accommodate variations between mAbs? Is it possible to develop a purification platform for various classes of products (e.g., mAbs and enzyme products)?

Atkinson (Cook): Platform purification processes must deal with both process- and product-related impurities. With antibody processes, the process-related impurities tend to dominate the development of the platform. Removal of host cell proteins (HCP), in particular, is usually a primary driver.

For the product-related impurities, most antibody processes are usually dominated by the removal of higher-molecular weight aggregates, followed by clipped forms and other charge variants. This is why so many platforms use an affinity step, followed by some combination of ion-exchange and/or mixed-mode separation.

It is important to note that a platform process for purifying antibodies must ac-

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commodate both charge and hydrophobicity variation between the molecules themselves. The constant regions of most immunoglobulins is consistent in physical and chemical behavior, but single amino acid changes in variable regions can drastically shift either the isoelectric point (pI) of the protein or the relative regional hydrophobicity. So the process must be able to remove a wide range of charge variants as well as various hydrophobic species (e.g., aggregates.)

Moesta (Bristol-Myers): mAbs, Fc-fusion proteins and adnectins developed by Bristol-Myers Squibb have large conserved regions, resulting in physical properties that allow one to achieve the vast majority of purification using platform technology. Charge heterogeneity in the variable region and post-translational modifications then require individually optimized polishing steps. For antibodies, this is usually a combination of an anion exchange step (either in flow-through or bind and elute mode) coupled with a second chromatography step. One must evaluate the remaining purification objective, select the best method, and optimize it. Viral inactivation and filtration steps, as well as diafiltration and concentration steps can be standardized and made to fit with a drug-product formulation platform if available.

"Scaling up, as opposed to out, is the preferred approach.," —Jim Powell, Asahi Kasei Bioprocess

PharmTech: Is it possible to develop a purification platform for various classes of products (e.g., mAbs and enzyme products)?

Atkinson (Cook): The challenge in developing platform processes that cover various classes grows as molecular diversity grows. Antibody and antibody-like fusion proteins can be treated as a broad class, but enzymes and other recombinant proteins will have very different molecular characteristics. So outside of broad platform generalities, such as no more than 3-4 columns, all aqueous processing with standard buffers and salts, standard viral filtration systems, and so forth, the platforms will otherwise most likely be quite divergent for different classes of proteins.

PharmTech: Can purification platforms accommodate the rising titers that upstream processes are yielding?

Atkinson (Cook): The rising titers are both a blessing and a curse for downstream unit productivity. The capacity of most chromatography resins is basically sufficient for the increased titers, but the buffer consumption and the throughput become a challenge with very high titers. In this case, limiting the number of unit operations, for example, moving from a three-column antibody process to a two-column process

becomes much more attractive. Engineering solutions, such as buffer blending and even possibly simulated-moving bed chromatography can also be considered to manage the increased productivity.

Most downstream unit operations, with the exception of viral filtration, are inherently scalable to an industrial scale. I believe that the biggest downstream bottleneck for high-titer processes has become viral filtration. Most chromatography unit operations can scale effectively, but the need to use an expensive, low-throughput filter can create an inefficient bottleneck in the overall purification process for mammalian cell-derived products.

Scale-up challenges include the high upfront cost for consumables (e.g. resins, bags, filters) as well as the challenges with liquid handling. Bulk volumes of liquid and intermediate holds are inherently inefficient. Engineering solutions for liquid transfer, mixing, and minimizing storage of liquids should be explored.

Moesta (Bristol-Myers): The technology available today can accomplish the manufacture of proteins up to the metric-ton scale. However, few products to date require this large scale of manufacture.

Increasing demand for proteins, combined with higher titers in fermentation, can enable implementation of alternative technologies, such as protein precipitation and crystallization. These technologies provide a means to improve purification throughput while significantly reducing cost. Some examples include blood fractionation products and recombinant insulin.

A key scale-up challenge is chromatography because there are physical limits based on resin-flow characteristics (e.g., back pressure and compression). The next step for industry is the use of simulated moving-bed technology, which can increase throughput.

Powell (Asahi): Process engineers can accommodate rising titers using a combination of liquid handling systems and modern virus-removal filters. Because the ability to rapidly and reproducibly create accurate buffers in a minimal footprint is a common bottleneck during downstream processing, Asahi Kasei Bioprocess offers IBD inline buffer dilution systems to generate on-demand diluted buffers for capture, polishing, and virus-removal. Customized skids are easily integrated with existing equipment to improve purification efficiency.

Additionally, next-generation virus-removal filters facilitate reliable processing at concentrations of up to 50 g/L. Before processing high titers, basic physics of production must be considered. Such factors include the viscosity of the feed material, mechanism of mass transfer, and filter efficiency. Purification becomes easier as the ratio of contaminants to product decreases yet caution must be used as high product levels often reduce cell viability.

PharmTech: With regard to scale up, how do downstream process platforms perform? Are there limitations?

Moesta (Bristol-Myers): Large plants, such as Bristol-Myers' Devens plant in Massachu-

setts, can have long piping runs between pieces of equipment with significant hold-up volumes. If appropriately designed, process piping either drains by gravity or can be blown out with compressed air, minimizing losses. Filter housings often require water flushes for adequate yield recovery. If properly optimized, large-scale process performance can meet or exceed that observed at smaller scale.

Powell (Asahi): Scaling up, as opposed to out, is the preferred approach. During scale up, a facility transitions to larger diameter columns and filter housings before launching trains of production units in parallel. Besides reagent disposal, additional challenges include space as well as the use of water and buffer.

Holding tanks may be required for byproducts that cannot be released directly into the environment. However, properly designed chromatography systems from Asahi Kasei Bioprocess can reduce the ratio between the hold-up volume and the filter or liquid chromatography (LC) column volume to minimize the waste burden and improve operational efficiency.

PharmTech: Do these scale-up problems require customized solutions?

Powell (Asahi): Obstacles created by process scale up require customizes solutions to a certain extent, especially with respect to automation. When a company moves forward with commercial production, a plant-wide distributed control systems have historically been the preferred method to control and gather data from each step in the process. But for smaller scale production. such as orphan drugs, "islands of automation" are still preferable.

Finer, more accurate monitoring of this nature streamlines operations and enables tanks to open to skids at the proper time. Distributed control systems provide greater access to information in a manufacturing plant, thereby allowing euipment-related problems to be identified and addressed prior to impacting production.

PharmTech: Looking ahead, how can platform technologies for analytical methods be improved? Can methods for detecting contaminating proteins, host-cell proteins, and protein level be standardized? What new technologies or methods could help?

Atkinson (Cook): Analytical methods, by definition, should theoretically be amenable to platform standardization. As mentioned, the primary purpose is to detect process- and product-related impurities. The challenge for process-related impurities is that each upstream platform produces different impurities, such as type and amount of HCPs. Unfortunately 'generic' commercial kits are often poor substitutes for process-specific detection methods, but do serve a purpose when used consistently in a platform.

"Analytical methods, by definition, should theoretically be amenable to platform standardization," — Morrey Atkinson, Cook Pharmica

For product-related impurities, the challenge is similar to that for downstream processing, and depends on specific molecular variants. In addition, the analytical technologies employed are not yet standardized. Charge variants, for instance, can be detected by at least four different methods, none of which effectively discriminate amongst several types of variants (e.g., sialic acid content, deamidation).

If the platform methods are developed in parallel with the process, and used and controlled consistently, then they can be useful within the portfolio they are employed. Process-related impurities are better understood and controlled, and minor modifications can be made to address product-related impurities. However, the relative utility of the platform is lessened when applied more broadly across product portfolios.

Ideal analytical methods would both separate and identify unique molecular species. A high-throughput, quality-control friendly functional equivalent to an LC–MS method would be desirable.

Moesta (Bristol-Myers): Most straightforward analytical methods such as A280, capillary electrophoresis, polyacrylamide gel electrophoresis, isoelectric focusing, and size-exclusion high-performance liquid chromatography, are flexible and lend themselves for upstream and downstream analyses. More complex methodologies, particularly for unique post-translational modifications and potency, are not as easily standardized, particularly those requiring high-end analytical endpoints such as mass spectrometry (MS), nuclear magnetic resonance (NMR), surface plasmon resonance for binding kinetics, and cell-based bioassays.

Once projects progress to the clinical-trial stage, it is advisable to take a closer look at standardized methods and optimize them for the molecule at hand.

The first requirement for being able to facilitate the use of an analytical platform is that the master cell line, expression vector, and upstream and downstream process steps are standardized as much as possible. The better characterized and standardized the process, a combination of anti-sera reactive against known impurities and HCPs can be created from premade anti-contaminant libraries to provide sufficient coverage and sensitivity. Protein-A detection methods are relatively easy to platform while HCP methods tend to be the most challenging.

Newer surface-plasmon resonance instrumentation is providing for significant improvement in the throughput and robustness required for ligand binding and binding kinetics assays. With particular molecule classes (e.g., mAbs), standardization of common reagents and capture approaches can improve and simplify the method development of specific binding activity method platforms.

For cell-based bioassays (potency), the use of common cell-based systems, either off the shelf or specifically designed, and activity read-outs for classes of activities (e.g. cytokine production, cell migration, etc.), can significantly reduce the amount of *de novo* method development. Also, the standardization of read-outs such as chemiluminescence or enzyme-generated colorimetric measurements in a microtiter plate format can further improve throughput. **PT**

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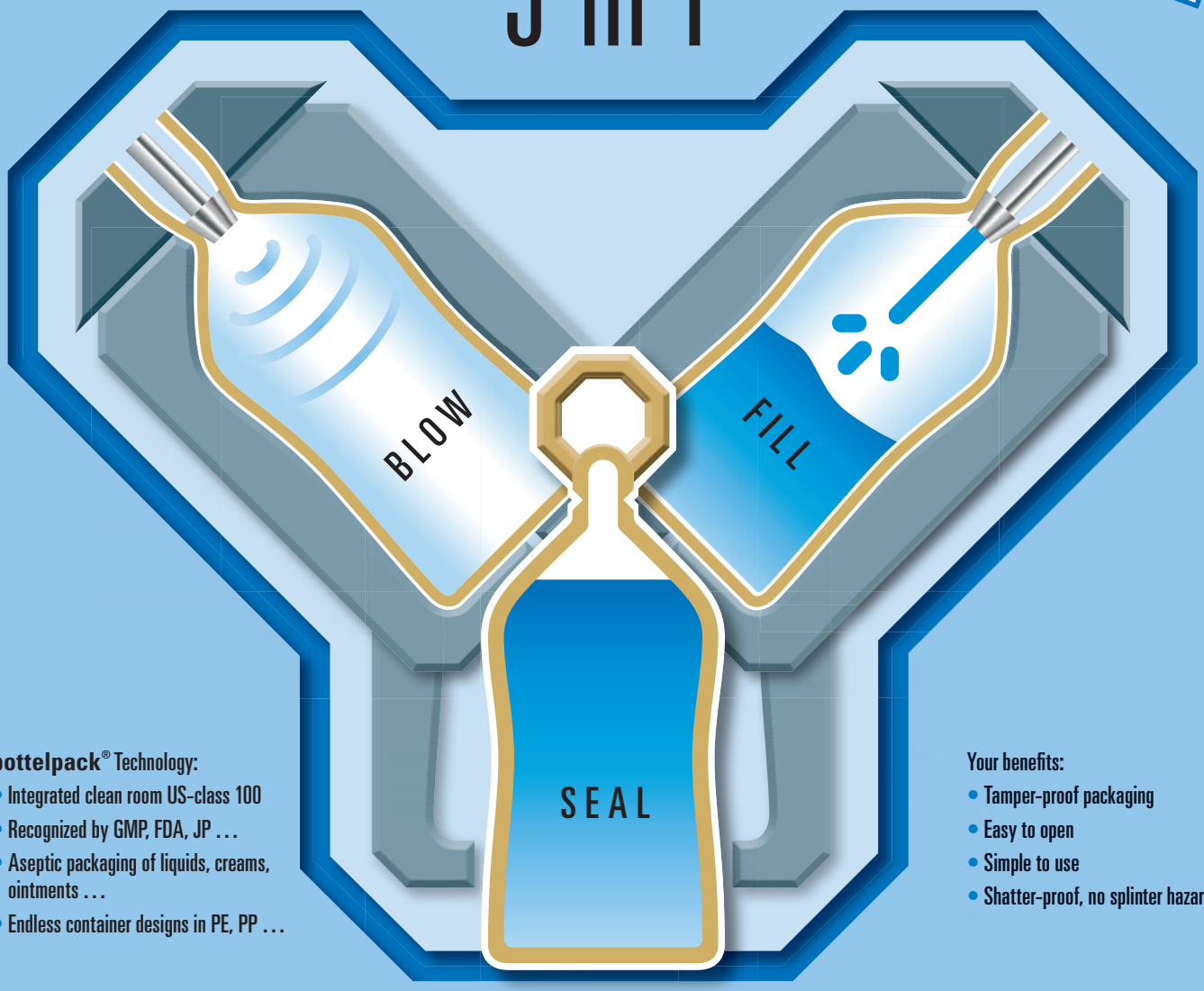

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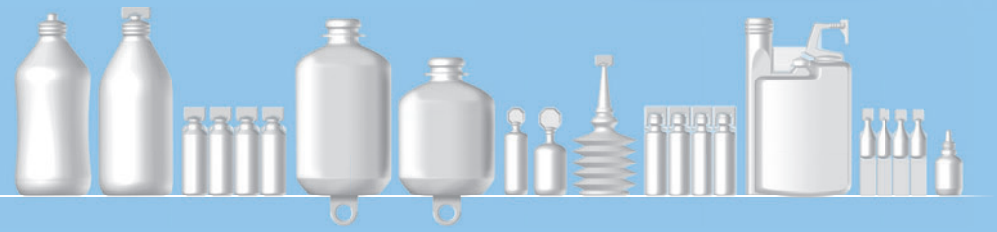

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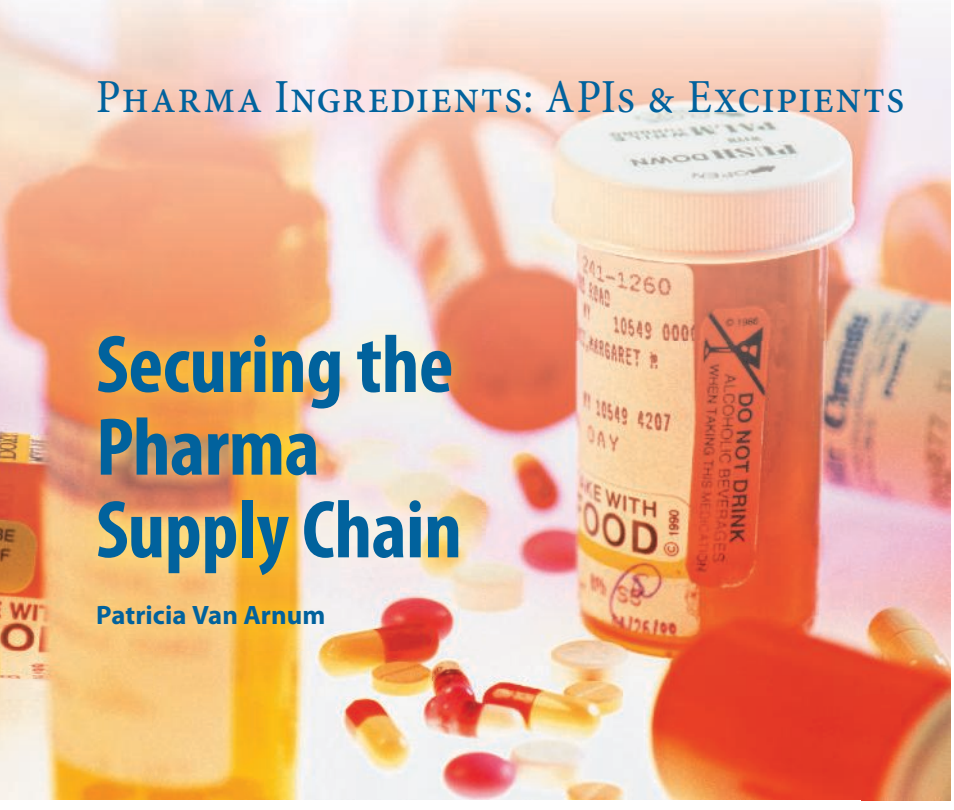


Securing the Pharma Supply Chain

Patricia Van Arnum

Regulatory bodies, standard-setting organizations, and industry seek to tackle the problem of counterfeit drugs and securing the flow of pharma ingredients.

Securing the pharmaceutical supply chain is of crucial importance to drug companies, suppliers, and consumers. The problem of supply-chain security has taken center stage with a number of recent initiatives.

Counterfeit drugs

Although the problem of counterfeit drugs traditionally has centered on solid dosage drugs, recent drug shortages for injectable cancer medications have triggered concerns over counterfeit versions of these types of drugs. In January 2012, FDA advised that current shortages of injectable cancer medications may present an opportunity for introduction of non-FDA approved products into the drug supply (1). FDA advised healthcare providers to obtain and use only FDA-approved injectable cancer medications purchased directly from the manufacturer or from wholesale distributors licensed in the United States.

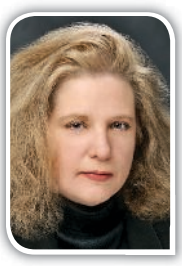
FDA advised in January 2012 of promotions and sales of unapproved injectable cancer medications direct-to-clinics in the US, which most likely were administered to patients. Products purchased include a high percentage of sterile injectable medications and medications whose quality could be adversely affected if they are not stored or transported under specific temperatures. Examples of products include unapproved versions of FDA-approved medications, such as Faslodex (fulvestrant), Neupogen (filgrastim), Rituxan (rituximab) and Herceptin (trastuzumab).

In certain circumstances, FDA may authorize limited importation of medications that are in short supply. Such medications are imported from approved international sources and distributed in the US through a controlled network and would not be sold in direct-to-clinic solicitations. If FDA has arranged for limited importation of the foreign version of a medication, information on obtaining that medication is available on the FDA drug shortages website (1).

FDA's notification in January was followed by another problem of a counterfeit version of an injectable drug, Avastin (bevacizumab). In mid-February 2012, FDA warned healthcare professionals and patients about a counterfeit version of Roche's/Genentech's anticancer drug Avastin 400 mg/16 mL, which may have been purchased and used by some medical practices in the US. Avastin is an injectable medicine and is administered to patients in clinics, hospitals, and doctors' offices. The counterfeit version of Avastin does not contain the medicine's active ingredient, bevacizumab, which may have resulted in patients not receiving needed therapy (2).

In a related action, FDA issued letters to 19 medical practices in the US that purchased unapproved cancer medicines that may include the counterfeit Avastin. The counterfeit version is labeled as Avastin, manufactured by Roche. Roche is the company that manufactures Avastin approved for marketing outside of the US. The only FDA-approved version of Avastin for use in the US is marketed by Genentech (a member company of Roche). The FDA-approved version does not include the Roche logo on the packaging or vials. In addition, Genentech's FDA-approved version of Avastin vials and packaging have a 6-digit numeric batch number and expiration dates in a three-letter month and four-digit year format (e.g., JAN 2014). Genentech's Avastin products are safe and effective for their intended uses.

The 19 medical practices in the United States purchased unapproved cancer medicines and, potentially, the counterfeit Avastin, from Quality Specialty Products (QSP), a foreign supplier that may also be known as Montana Health Care Solutions, according to FDA documentation (2). Volunteer Distribution in Gainesboro, Tennessee, is a distributor of QSP's products. FDA requested that the medical practices stop using any remaining products from these suppliers. FDA cannot ensure the safety or efficacy of any of these unapproved products. Based on information to date, FDA determined that none of the unapproved cancer medicines received by these medical practices from Volunteer Distribution are in shortage in the US. FDA-approved versions of



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Coordinating US efforts

In March 2011, several US government agencies and departments—FDA, the Office of the Intellectual Property Enforcement Coordinator, the US Customs and Border Protection (CBP), US Immigration and Customs Enforcement, the US Departments of Justice, State and Commerce, and the Agency for International Development—issued a joint report recommending a series of items to combat the problem of counterfeit medicines entering the US (3). The report called for better data and information-sharing among government agencies and departments to address counterfeit medicines entering the US. For example, as part of a process for developing an Import Operation Strategic Plan, FDA and CBP examined the flow of imported pharmaceutical products through different ports of entry, identified available legal authorities, and worked to develop best practices to enhance collaborative enforcement efforts. (3).

CBP and FDA are engaged in ways to ensure that only compliant pharmaceuticals are imported into the US and that appropriate enforcement action is taken against illegal pharmaceuticals. For example, FDA and CBP will explore ways to ensure that, under appropriate circumstances, products are destroyed rather than returned to the sender. CBP and FDA also are exploring ways to improve targeting of counterfeit pharmaceuticals. And CBP, in coordination with FDA, will access civil penalties to deter repeat offenders of importation of counterfeit medicines (3).

Part of this effort also involved the development of a Secure Supply Chain (SSC) pilot program by FDA's Center for Drug Evaluation and Research and Office of Regulatory Affairs. The program is part of FDA's risk-based approach to ensure the safety of imported drugs. The program is designed to help expedite shipments of drugs that meet the SCC pilot criteria because FDA has greater confidence in the drugs that are imported by a company in control of its supply chain.

The Counterfeit Pharmaceutical Inter-Agency Working Group Report also called for increased measures for improving coordination among international bodies for combating counterfeit medicines, improving public awareness of counterfeit medicines, and improving government-to-government enforcement training. The report also called for continued involvement and support by FDA in the World Health Organization's International Medical Product Anti-counterfeiting Task Force (IMPACT). IMPACT brings together private and public sector experts to address the public health aspects of drug counterfeiting and is developing technical tools for countries to use and adopt to fight drug counterfeiting. These tools can be used to strengthen legislative, regulatory, technological, enforcement and communication infrastructure and build capacity for surveillance, identification, and prevention of counterfeit drugs from reaching patients. (3).

WHO and FDA are collaborating to build global rapid alert surveillance/moni-

Formulation development forum: programmable, wirelessly controlled microchips for drug delivery

Patient compliance is important when developing a drug-delivery system, particularly when treating chronic diseases that require daily administration. Researchers at the Massachusetts Institute of Technology (MIT) recently reported on an alternative to daily injections: a programmable, wirelessly controlled microchip with an implantable device that allows drugs to be released inside the body without percutaneous connections in or on the patient. An implantable microchip device also offers the potential for real-time dose schedule-tracking and for physicians to remotely adjust treatment schedules.

The MIT researchers reported positive results of a human clinical trial using such a device. The primary objective of the rial was to assess the pharmacokinetics (PK) of the released drug, teriparatide, from the implanted devices. Safety measures included evaluating the biological response to the implant and monitoring indicators of toxicity. Secondary objectives were to assess the bioactivity of the drug and to evaluate the reliability and reproducibility of releasing the drug from the device.

In the trial, human teriparatide, a parathyroid hormone fragment [hPTH(1-34)] and anabolic osteoporosis treatment, was delivered from the device *in vivo*. The microchip-based devices contained discrete doses of lyophilized hPTH(1-34) and were implanted in eight osteoporotic postmenopausal women for four months and wirelessly programmed to release doses from the device once daily for up to 20 days. A computer-based programmer, operating in the Medical Implant Communications Service band, established a bidirectional wireless communication link with the implant to program the dosing schedule and receive implant status confirming proper operation. Each woman subsequently received hPTH(1-34) injections in escalating doses (1). The human trial began in Denmark in January 2011. The chips used in the study stored 20 doses of teriparatide, individually sealed in reservoirs capped with a thin layer of platinum and titanium that melted when a small electric current was applied, thereby releasing the drug.

The device and drug combination were found to be biocompatible with no adverse immune reaction. The resulting PK profiles from the implant were comparable to and had less variation than the PK profiles of multiple, recommended subcutaneous injections of teriparatide. The study also demonstrated that the programmable implant was able to deliver the drug at scheduled intervals. Drug delivery and evaluation in patients occurred over a one-month period and provided proof-of-concept measures of drug release and device durability that support implantable device viability for 12 months or more, according to a Feb. 16, 2012, press release of MicroCHIPS, which has licensed the technology from MIT. The MIT researchers began work on the implantable chip in the 1990s (2).

The microchip-based implants can sense biochemical changes, deliver drug therapies, and wirelessly communicate status to networked patients and clinicians. The technologies use microreservoir arrays to hermetically store and protect pharmaceuticals or sensors for extended periods of time. The microchip is controlled by microprocessors, wireless communications, or sensor feedback loops for dynamic control of drug delivery or sensing. MicroCHIPS is developing new designs of its microchip-based implant to include as many as 400 doses per device for providing daily dosing for one year or multiyear therapy for less frequent dosing regimens.

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toring systems for combating counterfeit and falsified medicines and risks in supply-chain security. The goals of this effort are to generate sound and reliable evidence of where the incidence of falsified medicines is most serious, and promote exchange of information (e.g., case reports and descriptions of actions taken) and expertise between countries to stimulate action. Also, FDA and WHO are partnering to make available a system to be used for collecting and disseminating information based upon the requirements shared by all partners (3).

USP efforts

In January 2012, the US Pharmacopeial Convention (USP) proposed a set of recommended best practices to help ensure that medicines can be traced back to their original manufacturer, are not adulterated or counterfeited, and are transported to their intended destination with their quality intact. USP is seeking broad feedback on these recommendations on supply-chain integrity. The new standard being proposed is not mandatory and is contained in the proposed USP General Chapter <1083> *Good Distribution Practices—Supply Chain Integrity.* The proposal is intended to serve as a central guidance document outlining the essential elements of an effective strategy.

"While individual pharmaceutical companies have their own approaches to addressing this issue, the size and sophistication of companies and their suppliers vary widely, as do their quality systems and risk management approaches," noted USP in a Jan. 4, 2012, press release in announcing the proposed standard. "Broad consensus around issues such as track-and-trace technology does not exist, and smaller companies that may be relied upon for sourcing pharmaceutical ingredients may or may not have security approaches comparable to their larger counterparts. Supply-chain integrity involves minimizing risks that arise anywhere along the supply chain, from sourcing pharmaceutical raw materials to their manufacture and distribution," noted USP in its release.

"There is incentive for all players in the pharmaceutical industry—large and small companies, regulators and standards-setting bodies—to come to some agreement on hot-button issues such as track-and-trace technology and, at the larger level, to codify what constitutes a solid, universal approach to global supply-chain integrity," said Praveen Tyle, chief science officer for USP, in the release. "USP has developed an initial proposal that we expect to evolve as industry, FDA and others weigh in. Our role as an independent body provides an opportunity to convene all these parties and advance this critical issue. While some pockets of information are available via FDA guidances, trade organizations and other sources, an overall approach is lacking. USP can move forward something more concrete than a technical report, as part of a mechanism that can be regularly updated to best meet the needs of all."

The proposed standard covers four main areas:

- *Importation*—Details three primary initiatives importers should undertake to help prevent and detect potential risks: supply-chain risk management, development of effective supplier partnerships and building a supply-chain quality system
- *Counterfeit drugs and medical devices*—Documents types of counterfeit drugs, medical consequences, and distribution and extent of counterfeit drugs and devices
- *Best practices to combat counterfeit drug and medical devices*—Covers topics including packaging technologies (tamper-evident designs, authentication technologies and serialization); drug pedigrees; machine-readable data carriers (2D bar codes and RFID tags); repackaging guidance, information retention and security; international standards; and best anticounterfeiting practices.
- *Diversion and theft*—Addresses factors that raise the risk of theft of drug products, drug components and medical devices; security systems, devices and procedures that should be implemented to reduce risk; and critical information to be gathered following discovery of a theft.

USP envisions the general chapter will be of use to all organizations and individuals involved in the global supply chain, including manufacturers; transportation companies involved in automobile, truck, rail, sea and air services; third-party logistics providers, freight forwarders and consolidators; brokers, importers, and exporters; packaging and repackaging operations; wholesalers and distributors; retail, mail-order, hospital, nursing home and other pharmacies; and mail distributors, including the US Postal Service and other expedited shipping services.

The formal proposal will be published in *Pharmacopeial Forum* **38** (2), March–April 2012. This is the vehicle through which USP accepts public comment on its standards. The draft general chapter and comments submitted to USP will be a central topic of a Supply Chain Integrity Workshop that USP is convening May 22–23, 2012, in Rockville, Maryland. This meeting will be a further opportunity to provide input, including whether additional information needs to be included in the chapter.

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DCAT Roundup: Podcast

Joan Connolly, president of the Drug, Chemical and Associated Technologies Assocation (DCAT) and principal of Connovan Consulting, talks to Patricia Van Arnum, executive editor, *Pharmaceutical Technology* and *Pharmaceutical Technology Europe*, about DCAT's goals and activities. Listen to the interview at PharmTech.Com/Podcasts.

Evaluating Impurities in Drugs

Part II of III

Kashyap R. Wadekar, Mitali Bhalme, S. Srinivasa Rao, K. Vigneshwar Reddy, L. Sampath Kumar, E. Balasubrahmanyam, and Ponnaiah Ravi

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The health implications of drug impurities can be significant because of potential teratogenic, mutagenic, or carcinogenic effects. Controlling and monitoring impurities in APIs and finished drug products, therefore, is a crucial issue in drug development and manufacturing, In Part II of this article, the authors examine impurities from chiral molecules, polymorphic contaminants, and genotoxic impurities.

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The public and the pharmaceutical industry are placing greater attention on impurities in drug as evidenced by the attention given to pharmaceutical impurities in books, journal articles, and national and international guidelines (1–10). The health implications of impurities can be significant because of their potential teratogenic, mutagenic, or carcinogenic effects. Controlling and monitoring impurities in APIs and finished drug products, therefore, is a crucial issue in drug development and manufacturing.

Part I of this article, which appeared in the February 2012 issue of *Pharmaceutical Technology*, discussed the various types and sources of impurities with specific case studies (11). This article, Part II, discusses chiral, polymorphic, and genotoxic impurities (12, 13). Part III, to be published in the April 2012 issue of *Pharmaceutical Technology*, will examine various degradation routes of APIs, impurities arising from API–excipient interaction during formulation, metabolite impurities, various analytical methodologies to measure impurity levels, and measures to control impurities.

Chiral impurities

Impurities can be present in the enantiomers of chiral compounds. Differences in pharmacological and toxicological profiles have been observed with chiral impurities *in vivo* (14, 15). The significance of stereochemical purity may be illustrated by formoterol, a selective β2-adrenoceptor agonist (16). This compound contains two chiral centers. Initial investigations indicated that the β2-agonist activity resided in the stereoisomer with the (*R*, *R*) absolute configuration with a rank order of potency (*R*, *R*) > (*R*, *S*) > (*S*, *S*) > (*S*, *R*). Subsequent investigation reported much greater difference with the eudismic ratio *R*, *R*/*S*, *S* increasing from 50 to 850 when the impurity of the eutomer in the diastereomer decreased from approximately 1.5 % to < 0.1% (17). Similar examples of stereochemical isomers can be found in the stereospecific drugs of the (*S*)-enantiomer of α-methyldopa, picenadol, (*R*)-sopromidine, (+)-(*S*)-apomorphine, and sertraline (18–24).

Another example is asenapine maleate, an antipsychotic belonging to the dibenzo-oxepino pyrroles class. Based on its receptor pharmacology, the efficacy is thought to be mediated by its antagonist activity on dopamine (D)-2 and

serotonin (5-HT)–2A receptors (25). Asenapine shows geometric isomerism and is a racemate of (+) and (-) enantiomers. It shows comparable binding affinities, meaning *trans*-asenapine showed higher affinity at D4 receptors than (+)/*cis*-asenapine (26).

Differences in pharmacological and toxicological profiles have been observed with chiral impurities *in vivo*, suggesting that chiral impurities should be monitored carefully. Although development of chiral drugs as single stereoisomers is a preferred approach, consideration must be given to unwanted stereoisomers, which may be present as impurities or degradants in the drug substance or drug product or generated through metabolism in biological systems. Chiral impurities in pharmaceutical samples may occur as side-products of the synthetic process as a result of an inversion of chiral centers due to chemical degradation of the drug substance or both. Similarly, inversion of the chiral center may occur *in vivo* as a result of metabolism, chemical degradation, or both.

Guidelines on the development of chiral compounds are published by regulatory authorities around the world, but they can be general and leave room for interpretation. The issues involved in chiral drug development are complex, and a coordinated approach among the many R&D groups is necessary. A multidisciplinary approach serves as a guide to the development of chiral compounds by coordinating research efforts in the various phases of development (22–36).

Polymorphic impurities

Polymorphism, the ability of a compound to exist in more than one crystalline form, affects the physical, chemical, and biological properties of a compound in question (37). These properties may influence several issues in pharmaceutical systems, such as processing characteristics, drug stability, and bioavailability. Demonstrating an understanding of the polymorphs in a given drug is an area of regulatory scrutiny in new drug applications (38).

The International Conference on Harmonization's Q6A guideline, *Specification: Test Procedure and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances*, outlines when and how polymorphic forms should be monitored and controlled (39). For stability concerns, the most stable form is normally used in the formulation. The metastable polymorphic form, however, may be inadvertently generated due to temperature, mechanical treatment, and moisture during processing or storage of the drug product (40).

Contamination of polymorphic impurities can adversely influence the stability and performance of the final drug product. Moreover, FDA requires development of validated methods for analysis of the proportion of crystalline forms throughout the drug's retest period and shelf life (41).

For example, olanzapine crystallizes in more than 25 crystalline forms, of which Form II has been designated

the most stable form and is used in the dosage form (42, 43). Olanzapine discolors in the presence of air (44). Polymorphic Forms I and II show very minor differences in their diffractograms. Evaluating olanzapine Form I for the presence of Form II, therefore, becomes very important.

Salmeterol xinafoate is known to exist in two crystalline polymorphic forms, with Form I being stable and Form II being the metastable polymorph under ambient conditions (45). These polymorphs have been characterized using differential scanning calorimetry, X-ray powder diffractometry, thermogravimetric analysis, and inverse gas chromatography (46). Commercial salmeterol xinafoate is a micronized form with the same crystal structure as that of Form I. The commercial drug, however, can contain traces of the Form II polymorph that is formed during the micronization process.

Exceptional case impurities

When a new process is developed, such as to overcome patent issues, it generally begins with new key starting materials, intermediates, reagents, or solvents that may react differently to give byproducts or process impurities. For example, in the synthesis of linezolid and pemetrexed disodium, several process impurities can be formed due to different process approaches.

Pharmaceutical companies can develop new processes based on raw materials, solvents, reagents, process conditions (i.e., temperature), and new polymorphs. Using new materials or processes, they may encounter several impurities that may not have been not present in the basic or initial synthesis of an API. After publication of monographs in the *United States Pharmacopeia*, *European Pharmacopoeia*, *British Pharmacopoeia*, *Indian Pharmacopoeia*, and *Japanese Pharmacopoeia*, they may not have a control of those impurities that are formed due to different process approaches. After publication of the monograph, companies have to change the analytical method or control these impurities as non-pharmacopeial impurities, including genotoxic impurities, with separate analytical methods, such as high-performance liquid chromatography (HPLC) or gas chromatography (GC).

For example, during the synthesis of linezolid, impurities based on a bis-linezolid compound and a bis-benzyl impurity are formed due to the non-infringed patent process (47–49). Some published patents have different potential process impurities, which cannot be separated in a single HPLC method, and which result from synthetic routes different from the synthetic route in the basic patent (47–55).

Pemetrexed disodium heptahydrate, the API in Eli Lilly's Alimta, is a multi-targeted antifolate used to treat mesothelioma and a second-line treatment for non-small-cell lung cancer. Alimta also is under investigation for multiple other cancers (56). Each non-infringed process patent has different potential impurities (see Figure 1, Process Impurities 1, 2, 3, and 4) (57–60). It may not be possible to analyze these impurities in a single HPLC method.

Impurities due to the piperazine ring

The piperazine moiety is present in the chemical structure of more than 200 drugs. The biotransformation of the piperazine ring involves several well-known metabolic reactions, including *N*-oxidation, hydroxylation, *N*-dealkylation, and ring cleavages to *N*-substituted as well as *N*,*N*'-disubstituted ethylenediamines. In addition, several unexpected metabolic pathways have been reported for the piperazine ring: *N*-glucuronidation, *N*-sulfonation, formation of carbamoyl glucuronide, and glutathione adducts (61). Some compounds containing the piperazine ring indicate that the ring is normally metabolically stable when both nitrogen atoms are substituted with groups larger than ethyl.

The lack of partial degradation of the piperazine ring to form ethylenediamine in olanzapine (2-methyl-4-(4-methyl-1-piperazinyl)10H-thieno[2,3-

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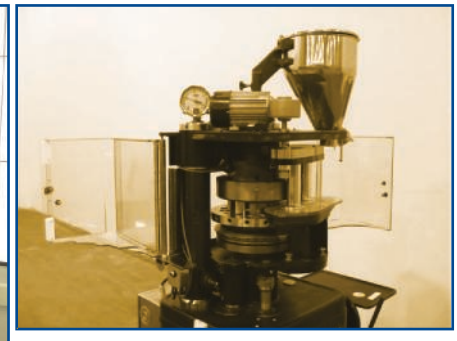

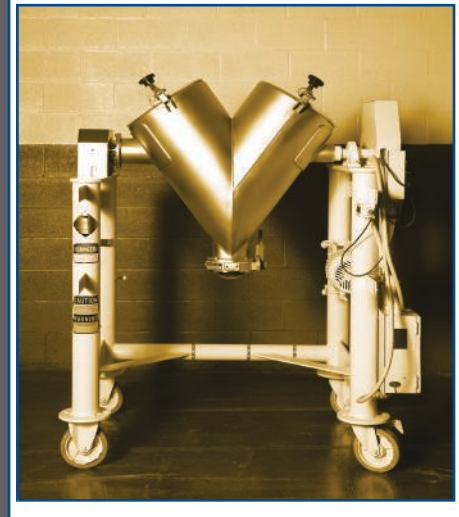

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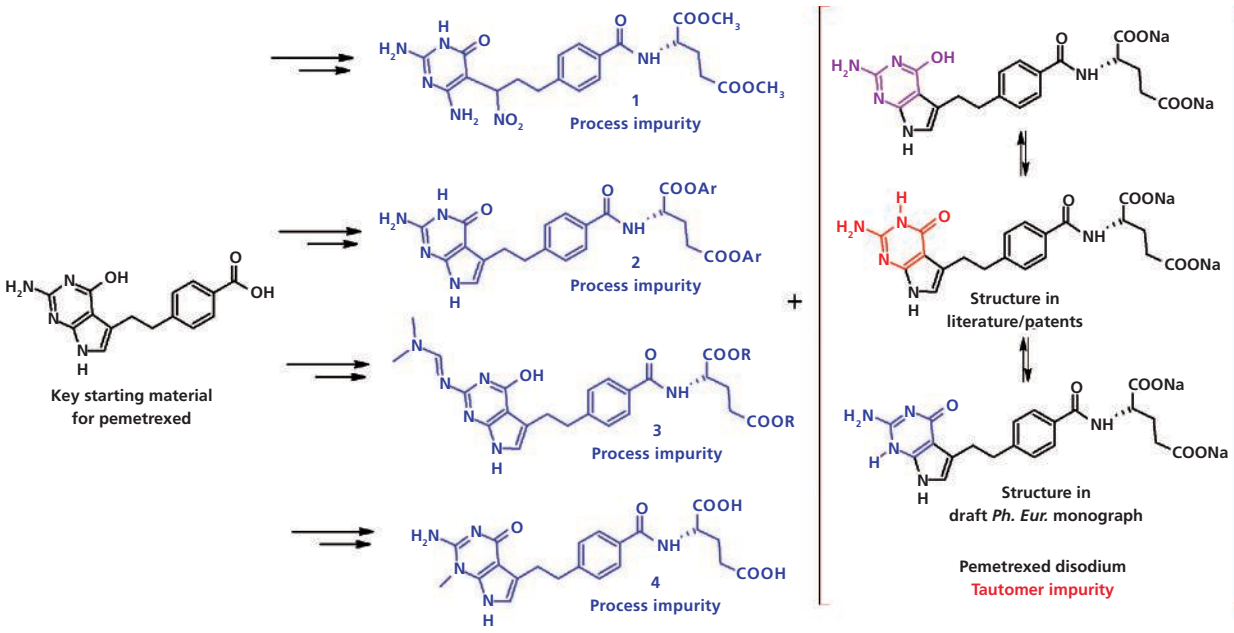
Figure 1: Reaction scheme for different process approaches for pemetrexed sodium impurities, respectively labeled as 1, 2, 3, and 4 (Refs. 57–60). *Ph. Eur.* is *European Pharmacopoeia*.



b][1,5]benzodiazepine) is slightly surprising. Some major metabolites were reported in humans plasma and urine, such as 4'-*N*-glucuronide and 4'-*N*-glucuronide (61, 62). Several other metabolites also were reported in mice, rats, monkeys, and dog urine (63). The ethylenediamine impurity, however, is not reported as a metabolite and a process impurity (see Figure 2).

When one of the nitrogen atoms is substituted by hydrogen on the piperazine ring, whether its methyl or ethyl, ethylenediamine formation is normally observed. An example is levofloxacin, *S*-(-)-9-fluoro-2,3-dihydro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-7H-pyrido[1,2,3-de][1,4] benzoxazine-6-carboxylic acid, which is the (*S*)-isomer of ofloxacin. In levofloxacin, the piperazine nitrogen atom is substituted with methyl due to several photodegradation impurities (see P 2 to P 10, Figure 3) (64–67). Some process impurities also are observed (see Figure 3). If the levofloxacin process involved methylenedichloride as a solvent, a chloro methyl impurity may form, and after isolation of the final product, the same impurity may convert to a di-quaternary cyclic piperazine impurity.

Additionally, when the ciprofloxacin (1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(piperazin-1-yl) quinoline-3-carboxylic acid) nitrogen atom is substituted by hydrogen on the piperazine ring, several metabolites and process impurities are formed (see Figure 3) (68–74). When nitrogen is substituted with hydrogen during the reaction, two dimer impurities (F-F dimer ciprofloxacin and F-Cl dimer ciprofloxacin) also are observed (75).

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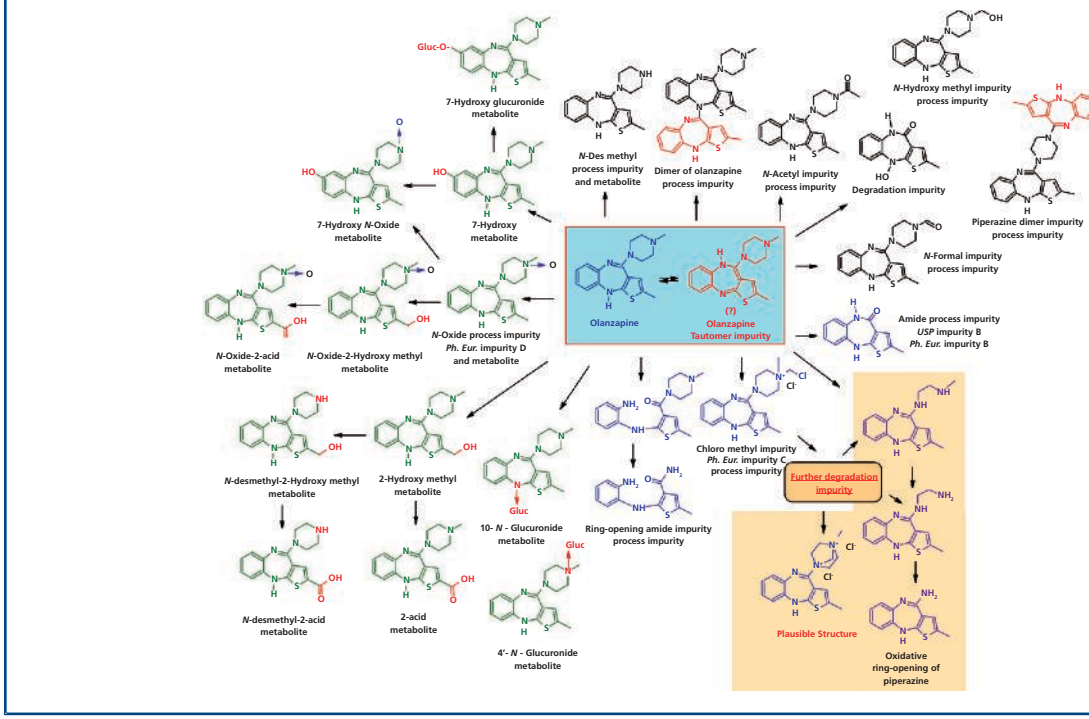
Figure 2: The piperazine ring and metabolite impurities of olanzanpine. *Ph. Eur.* is *European Pharmacopoeia*. *USP* is *US Pharmacopeia*.



Genotoxic impurities

There was no specific document on control of genotoxic impurities before 2000. ICH guidelines made passing references to compounds of unusual toxicity. Genotoxic impurities are chemical compounds that may be mutagenic and could potentially damage DNA (76). Non-monoalkylated agents are classified as genotoxic due to the nature of the functional groups they possess and also of related aniline derivatives. Additionally, salt-forming steps can introduce genotoxic impurities. Some examples include formation of methyl chloride as a side reaction of hydrochloric acid in methanol or esters of methanesulfonic acid as byproducts from the methanesulfonic acid salt-formation step in alcohol-based solvents (77, 78).

EMA issued guidelines on the threshold of toxicological concern (TTC) that recommended limits for exposure to potential genotoxic impurities to be 1.5 mcg per day for commercially approved drugs (79). As per the guidelines, testing will be required for all potential impurities from an API's synthetic route containing structural elements that are the cause of concern for genotoxicity potential using the well-established Salmonelle Ames test. The Ames test is a screening test that is used to help identify chemicals that affect the structure of DNA. The test exposes Salmonella bacteria to chemicals and looks for changes in the way bacteria grow. These changes result from mutations that occur when the structure of DNA is altered in certain places and the micronuclei test for mutagenicity (80, 81).

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Recommended qualification thresholds based on the maximum daily dose for drug substances and for drug products are provided in ICH Q3A and ICH Q3b (7, 8). The TTC data set was conducted from the perspective of an organic chemist who develops process technology for APIs (82). As part of the EMA guidance, API process designers are instructed to avoid all possible situations that could lead to the presence of impurities possessing genotoxic potential at any level in APIs.

During the establishing of the control mechanism, other factors, such as reactivity, solubility, and volatility, should be considered. Action should not be based only on the presence of alerting structures. It is important to make evaluations on a case-by-case basis, and precedence data should be considered, such as the stage of impurity formation, reactivity and carryover to the API, the intake of other routes, Ames test results, and data of closely related structures.

During process development, a genotoxic impurity may be introduced as a starting material, reagent, intermediate, catalyst, byproduct, isomer, or degradation product. (83). Alkyl halides used as reagents in synthesis are genotoxins (84). The same also was generated during chemical synthesis when a salt counter ion (e.g., hydrogen halide) of a drug substance reacts with alcohols when used as a solvent media.

The genotoxins ethyl chloride, methyl chloride, and isopropyl chloride were generated during the preparation of the hydrochloride salts of ethanol, methanol, and isopropyl alcohol (ICH listed solvents), respectively, at lower temperature (< 5 °C) as the key parameter of these impurities. In alcohol solvents, when HCl was 37% aqueous HCl or gas, it creates the maximum chance to form these alkyl halide impurities at trace levels. These impurities are detectable in GC at ppm level. Methane sulfonic acid (mesylate), benzene sulfonic acid (besylate) and *p*-toluenesulfonic acid (tosylate) are commonly used as counter ions to form API salts (85–87). Interactions of these acids with residual alcohols may lead to the generation of genotoxic impurities. Alkyl methane sulfonates, alkyl benzene sulfonates, and alkyl para-toluene sulfonates may combine with imatinib mesylate, amlodipine besylate, and denagliptin tosylate, respectively (88, 89).

The emphasis on genotoxic impurities is increasing, which creates challenges for both synthetic and analytical chemists, to develop sensitive and efficient methods to detect impurities at low levels (i.e., below TTC < 1.5 mcg/per day), which sometimes is not feasible and which increases the time and cost of drug development.

Linezolid (*S*)-*N*-[[3-[3-fluoro-4-(4-morpholinyl) phenyl]-2-oxo-5-oxazolidinyl]methyl]-acetamide, has genotoxic structural alerts and represents a new class of antibiotics, oxazolidinones. Forced-degradation studies are an important part of the drug-development process

Figure 3: The piperazine ring and metabolite impurities of levofloxacin and ciprofloxacin. *Ph. Eur.* is *European Pharmacopoeia* and *USP* is *US Pharmacopeia*. CAS No. refers to Chemical Abstracts Service (CAS) number.

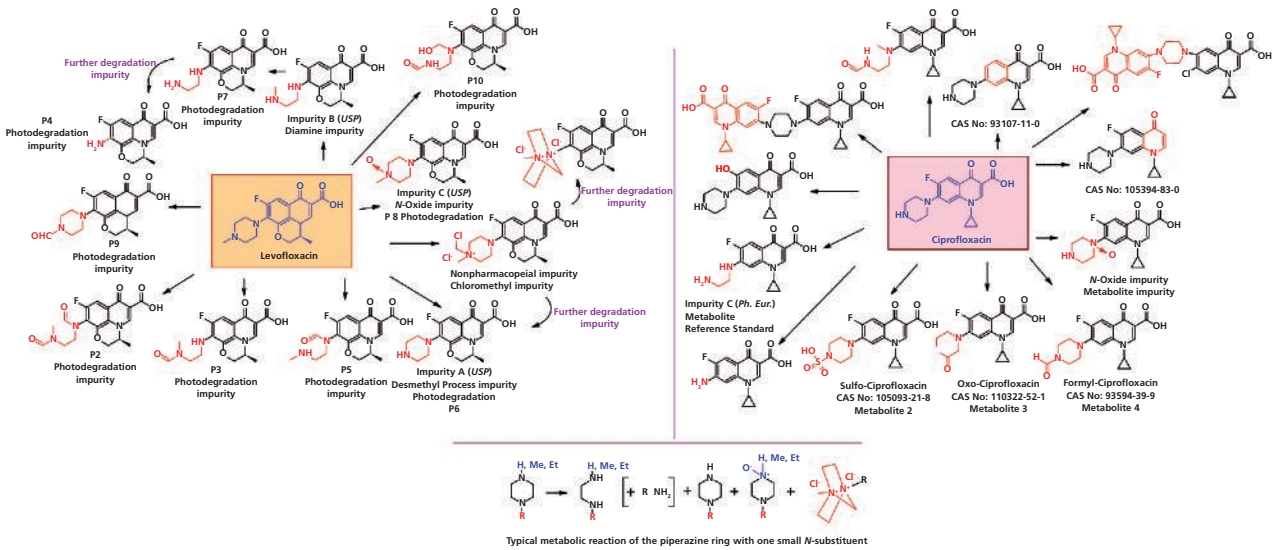
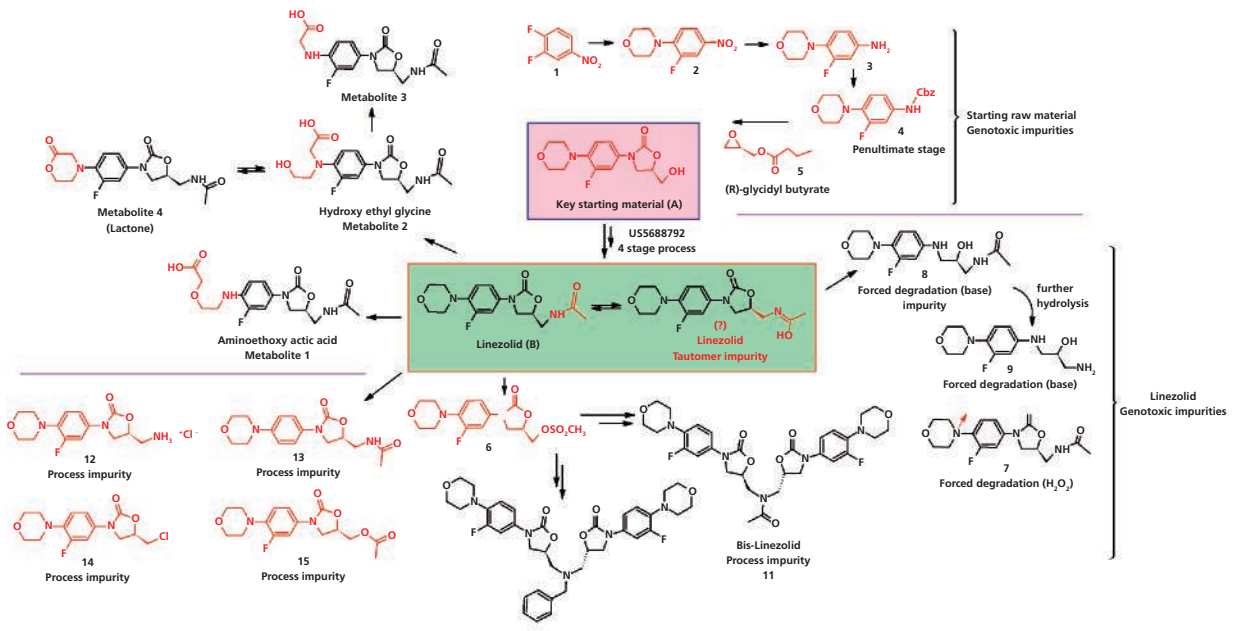


Figure 4: Process, genotoxic, and metabolite impurities of linezolid.



and are used increasingly in testing new molecules. These studies may give different impurities that may not be formed during process optimization and manufacturing validation, but these impurities must be controlled as per ICH guidelines. The authors have observed two impurities during a forced-degradation study in peroxide and alkaline conditions, Compounds 7, 8, and 9 (see Figure 4), which are structural alerts for genotoxicity, and which should be controlled so that the exposure to it is less than 1.5 mcg/day based on the maximum daily dose of the linezolid.

Linezolid's key starting material (A) shows genotoxicity alert and it contains five other intermediates, Compounds 1, 2, 3, 4, and 5 (see Figure 4). Compound A converts to the final drug, and it contains, Mesyl Impurity 6, Amine Impurity 12, Des Fluoro Impurity 13, Chloro Impurity 14, and O-Acetyl Impurity 15; these are the process impurities and have genotoxicity alert (49). During human studies, from the total amount of linezolid administered,

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only 30% was eliminated through the kidneys. Its major part was metabolized by oxidation of its morpholine ring, which resulted in the formation of two metabolites (see Figure 4): amino ethoxy acetic acid metabolite and hydroxy ethyl glycine metabolite (i.e., a major urinary metabolite) (90–92).

Conclusion

Part II of this article examined impurities that are associated with drug molecules having one or more chiral centers, APIs existing in various crystalline forms, drug substances with the piepererazine moiety, and APIs developed by new processes. Part II also looked into the extended application of the TTC to pharmaceuticals. To guarantee the quality and safety of pharmaceuticals during drug development, a quality concept has been proposed that adapts the ICH guidelines and which is focused on qualified impurity profiles.

Part III, to be published in the April 2012 issue of *Pharmaceutical Technology*, will examine various degradation routes of APIs, impurities arising from API–excipient interaction during formulation, metabolite impurities, various analytical methods to measure impurity levels, and measures to control impurities. Part I, published in the February issue of *Pharmaceutical Technology*, examined the types and sources of impurities (11).

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Monoclonal antibody formulation and lyophilization process development offer unique challenges based each individual molecule. Unexpected results can result in costly delays and significant formulation problems later in the development cycle. Applying Quality by Design (QbD) practices to formulation and development processes, early in the development cycle can lead to achieving development milestones faster and with more predictable results.

This 60-minute Webcast will offer insight from leading industry experts on QbD approaches to improve monoclonal antibody formulation and lyophilization process development. Gain insight into how development challenges can be minimized using QbD practices at the earliest stages of development.

Roman Hlodan, PhD, Biopharmaceutical Specialist at Patheon, will discuss QbD approaches to monoclonal antibodies formulation.

Enrico Corona, Formulation and Process Development Manager at Patheon, will present methods to include QbD processes for lyophilization cycle development.

WHO SHOULD ATTEND:

- Formulation scientists
- Formulation R&D managers, directors, and group leaders
- Process development scientists
- Process development managers, directors, and group leaders
- Section Heads
- Project Managers
- Technical personnel involved in process optimization
- Technical personnel involved in biologics formulation and development
- Scientists, manager, directors, and group leaders involved with lyophilization

Key Learning Objectives:

- How QbD approaches can improve monoclonal antibody formulation
- How QbD approaches can improve lyophilzation process development
- Case study illustrating how QbD practices improved downstream formulation stages

PRESENTERS

Roman Hlodan, PhD
Biopharmaceutical Specialist
Patheon

Enrico Corona
Formulation and Process Development Manager
Patheon

MODERATOR:

Angie Drakulich
Editorial Director
Pharmaceutical Technology

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Genotoxic Impurities

A Q&A with Amgen's Bo Shen

Moderated by Angie Drakulich

Genotoxic impurities and how to identify them and control for them have been a concern for several years in the pharmaceutical manufacturing industry. Pharmaceutical Technology spoke with Bo Shen, PhD, principal scientist at Amgen and chair of the AAPS Pharmaceutical Trace Impurities Focus Group, to gain insight on key challenges.

Genotoxic impurities and how to identify them and control for them have been a concern for several years in the pharmaceutical manufacturing industry. In recent years, FDA has issued draft guidance on the subject, EMA has issued final guidance, and the International Conference on Harmonization (ICH) is putting together a related M7 guideline to complement its Q3A and Q3B guidelines on impurities (1–3). Still, challenges remain. *Pharmaceutical Technology* spoke with Bo Shen, PhD, principal scientist at Amgen and chair of the American Association of Pharmaceutical Scientists (AAPS) Pharmaceutical Trace Impurities Focus Group, to gain insight on these challenges.

Key challenges and regulatory requirements

PharmTech: What would you say are the key challenges facing drug manufacturers today regarding genotoxic impurities (GTIs)? Is there still concern over FDA and EMA requirements/threshold limits or approaches for controlling for these impurities?

Shen: The identification of GTIs in pharmaceutical products, assessment of a safe level of exposure to these impurities, and establishing the corresponding limits are the key challenges and concerns still facing drug manufacturers.

Drug manufacturers have to identify GTIs early in process development, develop analytical methods, and demonstrate a control strategy to ensure patient safety. The assessment/identification phase involves a process by which the synthetic pathway is evaluated and through a combination of chemical reasoning and analytical testing, either known or potential genotoxic impurities (pGTIs) may be identified.

To assess pGTIs, drug manufacturers use a combination of *in-silico* tools, evaluate scientific literature and public databases, and may conduct an Ames test to determine the mutagenic potential of chemical compounds. The result of an Ames test takes precedent over the predictions made by *in-silico* programs. Of the *in vitro* genotoxicity tests, the Ames test is the most reliable predictor of carcinogencity.

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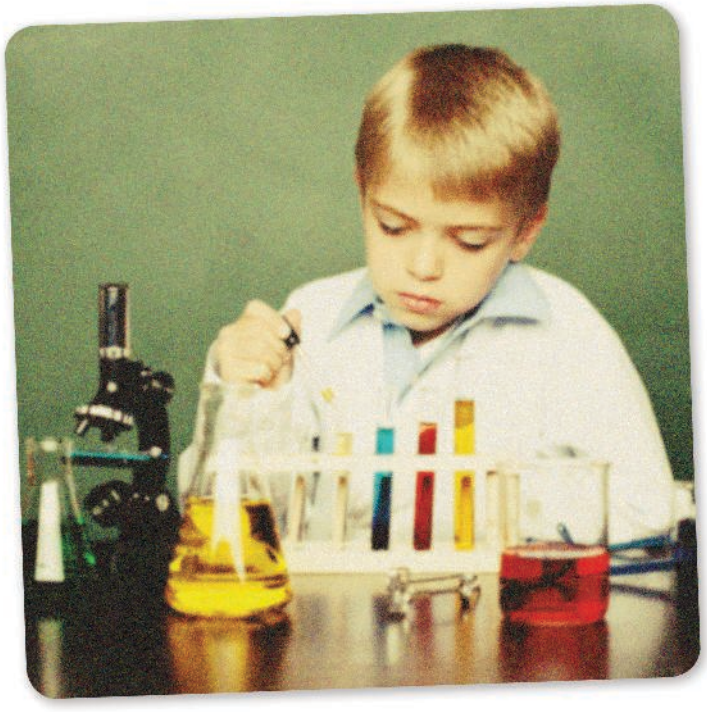

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Therefore, a compound that is positive in the Ames test is classified as genotoxic unless a substantial weight-of-evidence exists to conclude that the compound does not represent a genotoxic risk to patients.

To build such weight-of evidence involves conducting additional *in vitro* and *in vivo* gentoxicity tests that require significant resources and can lead to program delays if the GTIs cannot be controlled to the threshold of toxicological concern (TTC) while additional studies are being conducted.

Another challenge is that the Ames test may not be sensitive enough to detect GTIs when the impurity is assessed by testing the drug substance. The detection limit for many mutagens in the Ames test is 250 µg/plate, which represents a level far higher than is typically encountered for impurities in drug substances. Therefore, in many circumstances, the isolated impurity needs to be tested instead. Synthesis of an impurity in amounts and purity sufficient for Ames testing can provide a challenge to drug manufacturers.

After identifying GTIs, to ensure patient safety, drug manufacturers have to establish a robust control strategy to prevent or limit GTIs in the final API. Control strategy approaches will vary by companies. Some companies may choose to alter synthetic routes to avoid using or generating GTIs altogether; whereas, other companies may consider this impractical, especially when multiple GTIs must be handled and making changes might only lead to new ones.

The need of controlling several GTIs at the TTC level during analytical and process development further complicates the control strategy. Structural considerations can be complicated and numerous challenges can exist.

With the regulatory guidance in this area evolving and the need to ensure drug product quality and patient safety, drug manufacturers are faced with the challenge of effectively establishing and implementing robust internal practices which balance time, cost, and risk.

Analytical approaches

PharmTech: From an analytical-chemistry perspective, to meet current requirements regarding genotoxic impurities, how does it change the level, extent, or type of analytical testing that needs to be performed for an analysis of a particular active ingredient or finished drug product? Is typical impurity testing sufficient, or what additional testing or approaches may be required?

Shen: Consider the GTI control requirements, taking into account the TTC limit (1.5 µg/person/day) and the corresponding levels of the GTI in the drug substance, it can be calculated that for a daily dose of 1 g/person the limit for the GTI is 1.5 ppm and for a daily dose of 100 mg/person the corresponding limit is 15 ppm. This translates into target limits for GTI detection and quantification at levels of about 1 ppm, that is almost 500 times lower than those for classical impurity analysis (1 ppm versus 0.05%). Typical impurity testing is not suitable for GTI determination since their quantitation limit is generally 500 ppm (0.05%). Assessing multiple impurities in the low ppm range can be a significant analytical problem and challenge.

Liquid chromatography (LC) with ultraviolet (UV) detection and gas chromatography (GC) with flame ionization detection are often adequate for the impurities at 100 ppm level. In the range of 1–10 ppm or lower, hyphenated mass spectrometry (MS) techniques such as LC–MS and GC–MS are by far the most appropriate techniques. These techniques, due to sensitivity and selectivity, have been widely used in GTI analysis.

To build such weight-of evidence involves conducting additional in vitro and in vivo gentoxicity tests that require significant resources and can lead to program delays if the GTIs cannot be controlled.

In addition to sensitivity and specificity, other challenges in GTI analysis may include:

- Sample matrix interferences: techniques such as pre/post-treatment derivatization may be used to overcome these challenges.
- Analytes which are chemically reactive or unstable: special handling techniques may be required to overcome low recover or poor sensitivity.
- Analytes which are not suitable for common analytical detectors.

PharmTech: One of the FDA draft guidance recommendations on GTIs involves changing the synthetic or purification route to reduce or remove the impurity (1). Has this—or will this—become a challenge for drug manufacturers, particularly, if the synthesis of API involves intermediates or raw materials not internally produced and if these are be considered a source of the resulting impurity? If so, how is that addressed?

Shen: Changing synthetic routes or using purification could effectively avoid generating GTIs during the synthesis. However, route selection takes into account both yields and manufacturability considerations. Because of their intrinsic high reactivity, reactants and intermediates used in manufacturing processes may be genotoxic substances and it may not be suitable to avoid their use.

When changing synthetic routes is not feasible, pGTIs and GTIs are identified by a careful analysis of both the degradation products and the manufacturing process, taking

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into account reagents, intermediates and by-products. When the presence of a GTI is established, an explanation why no alternative to the use/formation of this impurity is possible (including alternate synthetic routes) should be provided as part of the pharmaceutical assessment. The technical effort aimed at reducing the GTI level according to ALARP, or as low as reasonably practical, should be documented. This latter part of the pharmaceutical assessment could give rise to some practical applicability issues.

For the intermediates or raw materials not internally produced, most companies are conducting rigorous testing to control impurities, or even establish specifications.

The focus group provides benefits to scientists by providing a single, broad forum to discuss technical and regulatory topics associated with impurities.

Industy's perpsepctive

PharmTech: What has been the role of the AAPS Pharmaceutical Trace Impurities Focus Group for genotoxic impurities on this issue?

Shen: The focus group provides benefits to pharmaceutical scientists by providing a single, broad forum to discuss technical and regulatory topics associated with the impurities, and to better understand at the grassroots level the practices, approaches, and trends used across the industry. Since its inception in 2010, the group has played an influential role on promoting scientific discussion for control and test strategy of genotoxic impurities. In the next few years, the group will continue to focus on highly sensitive analytical methodology development, process development, and genotoxicity tests for impurities/genotoxic impurities that are capable of controlling these impurities.

The group will effectively communicate to establish dialogues among industry, academia, and regulatory groups to discuss technical advances, and understand and apply changes in regulatory viewpoint on impurities/genotoxic impurities. The group will aim to facilitate discussion around science/risk-based regulations and regulatory review practice, and will work to catalyze opportunities to expand targeted academic support and collaborations on topics involving impurities/genotoxic impurities. Overall, the focus group offers a forum for discussion among researchers engaged in basic scientific work in analytical and process chemistry as well as toxicology, and serves as an outlet to connect with members of other sections and focus groups with related interests in the field.

The focus group routinely develops programming proposals in collaboration with other focus groups, such as the AAPS API Focus Group and other industry stakeholders, including the ICH M7 expert working group. For example, the focus group published the first industrial survey results about GTI and is in preparation and conducting a second industry survey on the methodology of the control of the GTIs. The AAPS focus group also organizes educational webinars and events.

These activities reflect the goals of the AAPS focus group, which include to:

- Establish a core group of interested scientists to explore diverse areas of genotoxic impurities and discuss technical and regulatory issues pertinent to genotoxic impurities
- Define technical and regulatory genotoxic impurities issues related to development of pharmaceuticals
- Provide a forum to discuss genotoxic impurities scientific issues and exchange ideas/best practices
- Organize quality programs for the annual meeting and to conduct workshops on current ICH and FDA and international requirements
- Provide an avenue for training of new guidance on impurities/genotoxic impurities topics
- Act as a link among members of industry, academia, and regulators
- Facilitate workshops/symposia and thereby share experiences and communicate key lessons learned with industry and regulators.

We welcome scientists and regulators to participate in the activities organized by the AAPS Pharmaceutical Trace Impurities Focus Group.

Acknowledgments

Bo Shen would like to specially thank Dr. Kurt Black, Dr. Ruth Lightfoot–Dunn, Dr. Jerry Murry, Dr. David Semin, and Dr. Sophie Wang for their review and input on this Q&A.

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A Holistic Approach to Supply-Chain Integrity

Anthony DeStefano and Desmond Hunt

US Pharmacopeia documents best supply-chain practices and seeks broad input on proposal.

One of the most daunting challenges facing pharmaceutical companies is securing the long and complex supply chains that are typical in today's global industry. From the sourcing of raw materials to final delivery to the pharmacy, practitioner or patient, the number of nodes in the global supply chain for a medicine is astounding, with each link presenting an opportunity for the insertion of risk or harm. Although most companies have highly sophisticated, multifaceted approaches to addressing this challenge, approaches vary.

In addition, there can be huge differences in approach not only between large and small or medium pharmaceutical manufacturers, but also among raw-materials suppliers, logistics providers, and the plethora of other companies involved in the production, distribution, and delivery of medicines to patients.

For example, many companies involved in the chain do not handle pharmaceuticals as their primary business. Despite the good work and due diligence that a pharmaceutical company, wholesale distributor, or other supply-chain stakeholder may employ, the effort can be rendered useless at the seemingly smallest breach. Wherever the breach occurs, someone may be there to take advantage. In the pharmaceutical supply chain, therefore, every step is important, and a company truly is only as strong as the weakest link.

Anthony DeStefano, PhD, is vice-president of general chapters, and **Desmond Hunt, PhD,** is a senior scientific liaison, both at the US Pharmacopeial Convention (USP).

To address this issue, the US Pharmacopeia (USP) recently published a proposed set of recommended best practices on supply-chain integrity, for which it is seeking broad input. If followed, these best practices will help ensure that medicines can be traced back to their original manufacturer, are not adulterated or counterfeited, and are transported to their intended destination with quality intact.

Despite the due diligence that a company may employ, the effort can be rendered useless at the seemingly smallest breach.

The proposal is contained in the draft *USP–NF* General Chapter <1083> "Good Distribution Practices—Supply Chain Integrity," which is published in the March–April *Pharmacopeial Forum (PF)* [38(2)].

Once in its final form, the general chapter will document what is envisioned to be a universal approach for helping to achieve supply-chain integrity. The general chapter is informational (i.e., nonmandatory), but USP hopes that the chapter can be a resource for companies that need to be brought up to speed on supply-chain issues and that it can serve as mechanism for building consensus across different industries.

Scope of the USP supply-chain chapter

The USP Packaging, Storage and Distribution Expert Committee, which is responsible for the new general chapter, has been interested in this topic for several years and sees the new proposal as one of an eventual suite of distribution chapters, following on the widely used General Chapter <1079> "Good Storage and Shipping Practices." Supply-chain integrity—which involves minimizing risks that arise anywhere along the supply chain—may be too broad for just one general chapter, however. That is one of the key questions USP has for industry and other stakeholders as it asks for feedback on the new chapter's contents.

USP expects the general chapter to evolve significantly from its draft, and hopes the public vetting will result in a strong final product that will be valuable to all relevant parties, including manufacturers; transportation companies involved in automobile, truck, rail, sea and air services; third-party logistics providers, freight forwarders and consolidators; brokers, importers and exporters; packaging and repackaging operations; wholesalers and distributors; retail, mail-order, hospital, nursing home

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and other pharmacies; and mail distributors, including the US Postal Service and other expedited shipping services.

The general chapter <1083> provides recommendations on how to minimize risk in international supply chains through effective partnerships and manufacturing quality systems. As it is written, the chapter covers four main areas:

- Importation, which details three primary initiatives importers should undertake to help prevent and detect potential risks (i.e., supply-chain risk management, development of effective supplier partnerships, and building a supply-chain quality system).
- Counterfeit Drugs and Medical Devices, which documents types of counterfeit drugs, medical consequences, and distribution and extent of counterfeit drugs and devices.
- Best Practices to Combat Counterfeit Drugs and Medical Devices, which covers packaging technologies (e.g., tamper-evident designs, authentication technologies and serialization); drug pedigrees; machine-readable data carriers (e.g., two-dimensional [2D] barcodes and radiofrequency identification [RFID] tags); repackaging guidance; information retention and security; best anticounterfeiting practices, and more.
- Diversion and Theft, which addresses factors that raise the risk of theft of drug products and components; security systems, devices, and procedures that should be implemented to reduce risk; and critical information to be gathered after a theft.

The practices included in the general chapter are top-level, and are purposefully nonprescriptive so as not to box companies in to one way of doing something. The general chapter intends to set a framework; companies can use the best approaches for them within that framework. When discussing track-and-trace technology, for instance, USP points to the two most widely recognized options: RFID and 2D barcodes. It is not, however, USP's role to decide on the actual technology to be implemented.

USP believes it can provide value as a convener of different stakeholders.

USP's role in supply-chain integrity

There has been much discussion in the industry regarding the challenges posed by a global supply chain, and yet, there are no overarching, comprehensive industry-wide practices to date. What does exist is piecemeal, with pockets of information available through FDA guidance, trade organizations, and other sources. USP believes it can provide value as a convener of different stakeholders. The organization can bring disparate views together and help organize the prevailing thoughts, finding commonalities among all players. In addition, through its inclusion in *USP–NF*—compendia widely recognized both domestically and internationally—recommendations put forth in a general chapter can have more weight than, for example, a technical report.

Finally, with *USP–NF* in a continuous state of revision, a mechanism exists for consistently updating the recommendations to reflect current realities. Because change is constant, USP's Expert Committee will be charged with monitoring whether there is a need for adapting the general chapter, thereby providing all parties with one central place for up-to-date information.

Industry participation

Given the complexity of this topic, USP is seeking extensive input from all the parties that have an interest in the new general chapter <1083>. Although the expert committee responsible for the chapter represents a diverse group of manufacturers, pharmacists, and other experts, USP is seeking additional perspectives to assist in providing a strong final product. The draft general chapter being published this spring may be deemed too broad or too specific, or may evolve into multiple chapters, for instance.

USP will evaluate all of these considerations based on feedback received from the diverse stakeholder community. In addition to comments obtained *via* the *PF*, USP is planning a Supply Chain Integrity Workshop at its headquarters in Rockville, MD, on May 22-23, 2012, to further solicit input. The workshop will seek to clarify USP's role in supply-chain integrity and address key topics such as related regulation and technology, and the roles and responsibilities of all parties in the supply chain. The workshop will have a strong international component as well. **PT**

More information about the workshop and general chapter can be viewed at www.usp.org.

Overcoming Challenges in Complex Formulation Development:

Bilayer Tablets & Beads-in-Capsules

LIVE WEBCAST: Tuesday, April 3, 2012 at 11:00 am EDT, 16:00 GMT

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EVENT OVERVIEW

Choosing the right formulation for a molecule is a challenging process. Whether you are looking to extend the life cycle of a drug or handling complicated APIs, there are multiple formulation options available for solid dose forms. Knowing which formulation will deliver the optimal results is crucial to a drug's eventual success. For example, how do you develop a fixed dose formulation that ensures the compatibility of multiple APIs with different profiles?

This 60-minute webcast will provide answers to questions such as these through case-study analysis and insight from leading industry experts on formulation-development strategies in product life-cycle management, including specialized formulations such as bilayer tablets and beads-in-capsules.

Anil Kane, Ph.D, MBA, Executive Director, Global Science & Technology, Pharmaceutical Development Services at Patheon, will discuss bilayer tableting challenges and solutions.

Ram Kasina Ph.D, Senior Director, Formulation and Process Development at Patheon, will discuss beads-in-capsule formulation-development challenges.

Key Learning Objectives:

- How to overcome formulation challenges with bilayer tablets
- How to overcome challenges in beads-in-capsule formulation development
- Case studies illustrating successful projects with bilayer tablets and beads-in-capsules

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- Process development scientists
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- Section heads
- Project managers
- Technical personnel involved in process optimization
- Technical personnel involved in formulation and development
- Scientists, managers, directors, and group leaders involved with formulation

Presenters

Anil Kane, Ph.D, MBA,
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Formulation and Process Development,
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Moderator:

Angie Drakulich,
Editorial Director,
Pharmaceutical Technology

For questions, contact Jamie Carpenter at jcarpenter@advanstar.com

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CMOs Face a Kodak Moment

Jim Miller

The evolving bio/pharmaceutical business model poses risk for CMOs.

Two fundamental cornerstones of the new bio/pharmaceutical business model are the end of the blockbuster product and the need to accumulate and conserve cash. These two realities have major implications for bio/pharmaceutical manufacturing strategies and technologies and create new challenges for CMOs.

It is widely understood and accepted that the new products coming out of the bio/pharmaceutical pipeline will be sold in smaller volumes than the products introduced a generation ago (albeit at higher prices). This situation partly reflects the failure of bio/pharmaceutical R&D laboratories to come up with safe and effective drugs suitable for broad populations. More importantly, it also reflects the growing understanding of how drug effectiveness varies within patient groups, the ability to develop biomarkers to identify patients for whom new drugs will work best, and the expectation of regulatory authorities that new drugs will incorporate that knowledge into clinical regimens. The classic example is Roche's/Genentech's Herceptin (trastuzumab), which is highly effectively for the 20% or so of breast-cancer patients that test positive for expressing the HER-2 gene.

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The need to accumulate and conserve cash is driven by the imperative that bio/pharmaceutical companies in-license or acquire new development candidates and marketed products rather than depend solely on their in-house R&D operations. One prime target for improving cash position is inventories. Bio/pharmaceutical companies have traditionally held two to four times as much inventory relative to sales as have consumer-products companies. Turning inventories more frequently can release hundreds of millions of dollars in cash for the large bio/pharmaceutical companies.

CMOs need to become more forward-looking about their technology.

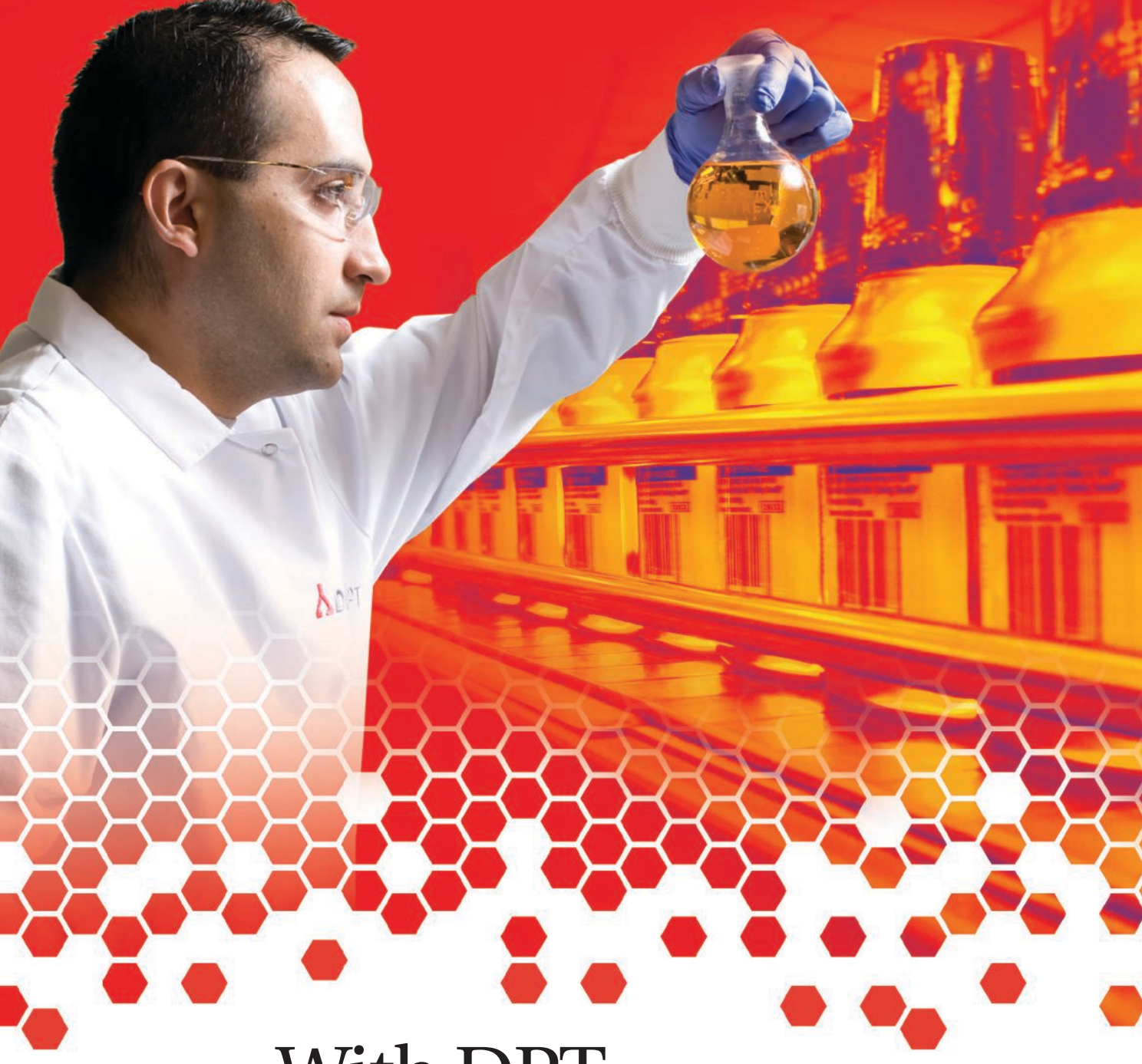
Small, frequent batches

The implication of these two realities—smaller volumes and faster inventory turns—is that bio/pharmaceutical companies must manufacture smaller batches more frequently than they have traditionally. This new manufacturing imperative is triggering major changes in manufacturing practices, strategies, and technology. For instance, the CEO of GlaxoSmithKline (GSK) recently talked about how GSK is shortening its supply chain (thereby reducing inventory requirements) by moving manufacturing closer to where the products are being sold rather than concentrating production in very large scale but distant manufacturing sites.

The new manufacturing paradigm will require facilities that are simultaneously smaller scale, more flexible, and lower cost and will mandate major changes in the design of facilities and equipment. Most of today's bio/pharmaceutical manufacturing facilities were designed 20 or more years ago to accommodate large-scale batch processing operations with separate suites each housing individual pieces of process equipment and complex material flows. Those facilities have very high fixed costs, and equipment often sits unutilized and requires long set-up times.

Pharmaceutical equipment manufacturers and companies that develop advanced manufacturing technologies have been responding to the new manufacturing requirements for some time. The major advances already being used include:

- Higher-yielding expression and fermentation technologies that reduce the scale of biomanufacturing facilities
- Manufacturing equipment for both API and dose manufacturing that incorporate disposable parts for components that come into contact with the product
- Microreactors for small-molecule API manufacture, which replace large-scale batch processes with continuous processes conducted in a single, small piece of equipment
- Continuous process finishing and dose manufacturing technologies,



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such as spray drying and equipment that can blend materials and extrude finished tablets
- FDA-endorsed methodologies, such as process analytical technology (PAT) and quality by design.

Some of these technologies and practices are not yet in widespread use or fully developed for commercial operation, but they are clearly making their way into the mainstream. For instance, Lonza announced in early February 2012 that it will build a "factory of the future" based on microreactor and continuous flow technology. Major bio/pharmaceutical companies are working with equipment suppliers and engineers to develop proprietary highly-automated and continuous manufacturing systems for their "factories of the future."

The new manufacturing paradigm will require facilities to be smaller scale, more flexible, and lower cost.

Challenge for CMOs

The changing bio/pharmaceutical manufacturing requirements and technologies present a major challenge to CMOs. Much of the manufacturing capacity of the dose CMO industry is compromised of legacy facilities acquired in the past 10 years from global bio/pharmaceutical companies and embodies the large-scale, inflexible, and high-cost batch manufacturing processes that were dominant 20 years ago. As the manufacturing needs of the bio/pharmaceutical industry evolve in the next 5–10 years, CMOs risk being left behind with underutilized facilities that are unsuited for their potential clients' needs.

Only a few CMOs can be considered innovators in manufacturing technology and practice despite the fact that manufacturing is only the thing they do. To a large degree, the CMO business forces them to focus on their clients' current and near-term needs. CMOs deal with a lot of older products and even with new products, their bio/pharmaceutical company clients are unwilling to take on the risk of new manufacturing technologies unless they absolutely have to. CMO profit margins generally do not allow much room for investment in innovation, and most innovative technologies housed at CMOs have been developed and paid for by their clients.

Unless CMOs become more forward-looking about their technology choices and investments, they risk losing out to new entrants and potential clients. The new technologies will often require less investment in facilities and utilities. Because they are smaller and more self-contained, more companies will be tempted to build their own facilities. Because they will operate more-or-less continuously and be highly automated, they will produce drugs less expensively than the older technologies.

Today, the competitive challenges that CMOs seem most focused on are how to differentiate themselves from their many North American and European competitors while keeping a wary eye on producers in emerging markets. By not appreciating the changing manufacturing requirements of their clients and the related new technologies, they risk being made obsolete.

This scenario bears a strong resemblance to what happened to Kodak, which recently filed for bankruptcy protection in the United States. Because it was focused on preserving its cash cow—the film and photo processing business—the company viewed its primary competitive threats as coming from Fujifilm and other low-cost film manufacturers. As a result, it overlooked the emergence of digital photography, the new technology that ultimately undermined the company. CMOs could now be facing their Kodak moment. **PT**

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Spirax Sarco Announces South Carolina Plant Expansion

Spirax Sarco is expanding its Blythewood, South Carolina, facility to accommodate growth in its steam-system solutions business. The new facility has over 35,800 ft^2 of office and production space.

"Our business is continually growing due to the hard work and dedication of our employees. This facility will enable Spirax Sarco to successfully meet the growing industry demand for steam system solutions and to better serve our customers nation-wide," said Stephen Gow, director of marketing.

Kerry to Expand Center of Excellence with New Cell Science Laboratory

Kerry Ingredients & Flavors, a provider of functional ingredients, is investing $10 million in expanding its Beloit, Wisconsin, facility to include a cell-science laboratory. The expansion will feature a consumer nutrition center, flavor laboratories, and product ideation and customer collaboration suites. The project is expected to be complete by August 2012, and will add an additional 30,000 ft^2 to the existing 260,000-ft^2 facility.

BMS Completes its Acquisition of Inhibitex

Bristol-Myers Squibb (BMS) has completed its $2.5-billion acquisition of the clinical-stage biotechnology company Inhibitex. The deal was valued at a purchase price of $26.00 per share. As of the expiration of the offer, 77,532,611 shares of common stock of Inhibitex were validly tendered and not withdrawn in the tender offer. As of the close of business on Feb. 10, 2012, approximately 4,260,705 shares remained subject to guaranteed delivery procedures.

Almac Doubles Analytical Capacity at its North American HQ

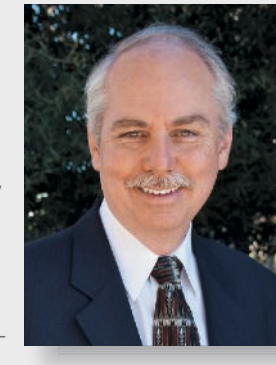
The CDMO Almac has announced that it is doubling its analytical capacity at its 240,000-ft^2 North American headquarters in Souderton, Pennsylvania. The facility offers full-service, integrated clinical packaging, drug-supply management, and technology services to pharmaceutical and biotechnology clients. Almac's additional laboratory investment will include polymorph and salt screening, and solid-form development. The new facility is also equipped with a bathless dissolution apparatus for comparative dissolution studies.

Amgen Agrees to Acquire Micromet

Amgen has agreed to acquire the biotechnology company Micromet for approximately $1.16 billion ($11 per share in cash). The transaction was unanimously approved by both companies' boards of directors and includes blinatumomab, a bispecific T-cell engager (BiTE) antibody in Phase II clinical development for treating acute lymphoblastic leukemia and non-Hodgkin's lymphoma, as well as proprietary BiTE antibody technology.

Q&A with

Chris Meissner, *president of Meissner Filtration Products*



PharmTech:
Do you see a new industry trend emerging?

Meissner:
There are many new industry trends, but very few have broad appeal that haven't already been discussed at some length. One trend that continues to be worth watching closely is how the industry continues to evolve as it faces a shrinking pipeline of promising new drugs, while also facing escalating R&D costs and increasing regulatory scrutiny. In recent years, the trend has been to partner with emerging biotechnology companies. As profitable drugs move off patent, companies are taking a second look at competing with generic competition by tackling that competition head on. They're investing in more efficient processes and, in some cases, even acquiring generic drug manufacturing companies. Key suppliers will also be expected to evolve and will be relied on to bring core competencies to bear more economically than in-house-derived solutions.

PharmTech:
How will the industry remain innovative as it reduces spending on research?

Meissner:
Spending less money on research actually increases the need for innovation rather than dampening it. The desire to fund only those projects that have the best chance of commercial success has always been high, but differentiating which of those projects are most likely to succeed remains a very difficult task. Additionally, the path to success with almost every project will likely be challenged at various times by obstacles that are best overcome with innovation.

Smaller, dynamic biotechnology firms have always relied on key suppliers to assist them with innovative solutions to overcome obstacles such as process bottlenecks. Now pharmaceutical companies of every size, many of whom have historically been vertically integrated from R&D through manufacturing, are increasingly relying on partners to conceive cost-effective solutions, effectively outsourcing many challenges. Our customers increasingly rely on us to enhance their R&D and manufacturing efficiency thereby stretching budgets as far as possible.

MANUFACTURING EQUIPMENT & SUPPLIES

Tablet press

Fette Compacting America's FE55 tablet press is equipped to handle 90% of common tablet formats. The FE55 can produce single- and double-layer tablets and perform direct pressing. The unit features punch stations that allow for a 50% output increase. **Fette Compacting America,** *Rockaway, NJ • www.fetteamerica.com • tel. 973.586.8722*

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*

Fluid-bed dryer

Federal Equipment offers a Vector fluid-bed dryer–granulator with a multipurpose Flo-Coater system. The unit has 316-L stainless steel product-contact surfaces, 20- and 60-L spray-granulation bowls with expansion chambers and guns, a two-bar internal shock rating, a top blow-out feature, an air-handling unit with filter, and a 15-hp blower. Other features include a dehumidification package, a dew-point monitor, and programmable logic controls. **Federal Equipment,** *Cleveland, OH • www.fedequip.com • tel. 216.271.3500*

MANUFACTURING EQUIPMENT & SUPPLIES

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*

Radar transmitter

The Magnetrol Eclipse Model 705 Guided Wave radar transmitter meets the requirements for wetted and nonwetted materials, process connections, and surface finishes for the hygienic industries. The Eclipse was designed to meet level-measurement-instrument needs for companies in the food and beverage, biopharmaceutical, and pharmaceutical industries. **Magnetrol Hygienic Measurement Solutions,** *Downers Grove, IL • www.magnetrol.com • tel. 800.624.8765*

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*

MANUFACTURING EQUIPMENT & SUPPLIES

Valve positioners

W.E. Anderson's Series 185 and 285 Smart Positioners use a 4- to 20-mA input signal to accurately control the valve stroke of linear valves. Observations of the positioners' condition are simplified with a standard liquid crystal display. Air-consumption levels remain minimal in order to reduce operating costs without reducing the performance of the device. **Dwyer Instruments,** *Michigan City, IN • www.dwyer-inst.com • tel. 800.872.9141*

Fluid-transfer stand

Meissner's stainless-steel FlexCessory stand is designed to secure and support FlexFill single-use fluid-transfer assemblies. The FlexCessory's sterile bottled liquids can be transferred to FlexFill for enhanced flexibility and security when adding fluids to either single or multiuse bioreactors. Excess fluid can be stored in the FlexFill biocontainer on the FlexCessory stand for future dispensing. **Meissner Filtration Products,** *Camarillo, CA • www.meissner.com • tel. 805.388.9911*

Laser-punch inspection system

LVS 500 uses dual-laser technology to provide immediate noncontact inspection of punches and interfaces with the Tool Management II (TM-II) database application for automatic data storage and analysis. The system is virtually maintenance-free and is designed specifically for tablet manufacturers. Visit natoli.com/LVS.html to schedule a free webinar. **Natoli Engineering Company,** *St. Charles, MO • www.natoli.com • tel. 636.926.8900*

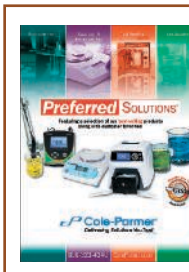
MANUFACTURING EQUIPMENT & SUPPLIES

Gravimetric feeder

The PureFeed DP-4 is a gravimetric feeder that meters dry pharmaceutical, nutraceutical, and cosmetic powders at feed rates as low as 20 g/h. A speed-controlled, inert ceramic-feed disc is positioned at the base of an electropolished stainless-steel material storage chamber to precisely rotate and discharge tiny amounts of material continuously over a 20- to 2000-g feed-rate range. **Schenck AccuRate,** *Whitewater, WI • www.accuratefeeders.com • tel. 888.742.1249*

Nominal prefilters

Sartoguard PES/GF 0.1- and 0.2-µm nominal prefilters combine clarification capabilities of glass-fiber layers with throughput performance of polyethersulfone membranes. The prefilters contain integrity-testable features and are bacterially retentive to a log-reduction value of 6/cm^2. Sartoguard is intended for biopharmaceutical applications such as media prefiltration and bioburden reduction. **Sartorius Stedim Biotech,** *Bohemia, NY • www.sartorius-stedim.com • tel. 800.368.7178*



Product catalog

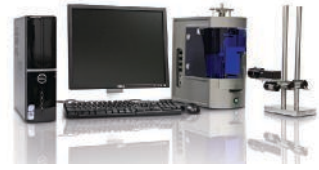
Cole-Parmer's 2012 Preferred Solutions catalog contains products for laboratories and process facilities, including circulating baths, pump systems, temperature meters, and spectrometers. The catalog contains 112 pages featuring brand names, such as Masterflex, Thermo Scientific, and Polystat. To request a free catalog, visit coleparmer.com/18996 or call 800.323.4340. **Cole-Parmer,** *Vernon Hills, IL • www.coleparmer.com • tel. 800.323.4340*

MANUFACTURING EQUIPMENT & SUPPLIES

SMI
Development · Delivery · Dependability

Tablet press

Specialty Measurement offers the MiniTab press, which is designed to manufacture tablets ranging from 0.5 to 4 mm in diameter. The introduction model can produce < 300,000 tablets/h; larger models will be capable of making > 2 million tablets/h. The compact size of the machine, less than 250 × 500 × 500 mm, makes it ideal for glove-box applications. **SMI,** *Lebanon, NJ • www.smitmc.com • tel. 908.534.1546*



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*

OUTSOURCING & CONSULTING SERVICES

Packaging films and anti-counterfeiting services

Bilcare Research offers packaging films such as polyvinyl chloride (PVC)–Mono, –PVDC, –Aclar, –AquaBa, and cold-form foil, as well as lidding foil-standard push-through aluminum foils, paperback child-resistant foils, and environmentally friendly lid foil Nova. Bilcare also offers formulation analysis, anticounterfeiting, and branding services, including Bilcare Protect. **Bilcare Research,** *Delaware City, DE • www.bilcaresolutions.com • tel. 302.838.4000*

OUTSOURCING & CONSULTING SERVICES

Contract services

Lonza provides services to the pharmaceutical, healthcare, and life-sciences industries. Lonza Custom Manufacturing's development and manufacturing services portfolio is designed to assist large and emerging biotechnology and pharmaceutical companies in improving and advancing their products. **Lonza,** *Basel • www.lonza.com • tel. +41 61 316 81 11*

Micron Technologies

Size reduction

Micron Technologies provides contract particle-size reduction and analytical services for the pharmaceutical industry. The company offers micronization and mechanical milling in isolated processing suites. Its analytical laboratory provides material-characterization testing, including particle size and Karl Fischer moisture analysis. Additional services include method development and validation and release and stability testing. **Micron Technologies,** *Malvern, PA • www.microntech.com • tel. 610.251.7440*

Outsourced services

Pfizer CentreSource provides solutions for sterile manufacturing, high-containment manufacturing, and oral and solid dosage forms. Its capabilities draw upon Pfizer's global network of facilities, technologies, and expertise to fulfill a broad range of sourcing and outsourcing requirements, regardless of dosage form, batch size, or the complexity of the process. **Pfizer CentreSource (PCS),** *Kalamazoo, MI • www.pfizercentresource.com • tel. 269.833.5844*

TOPICAL SEMI-SOLID FORMULATIONS

CMC Considerations for Stability, Analytical, and Safety Studies

LIVE WEBCAST: Thursday, March 22, 2012 at 1:00 PM EST

Register free at http://pharmtech.com/formulations

EVENT OVERVIEW:

Topical dermatological drugs are an important area of drug development for achieving local and systematic delivery. If your company is considering topical dermatological product development, this webcast provides an overview and specific examples of CMC (chemistry, manufacturing and controls) considerations for topical drug product development and how they might affect your IND or NDA submission. This webcast examines a range of 'real world' issues that analytical teams encounter during analytical method development/validation, stability studies, specification setting, and safety-study support for semi-solid formulations. Most importantly, draw your own lessons from multiple case studies of issues addressed during non-clinical/clinical stability programs and regulatory submissions. Case studies include stability-study design, analytical method development, specification development and proposed shelf-life, degradation-product evaluation, and integrated analytical support for safety studies.

Key Learning Objectives:

- Stability Studies—Understand important CMC considerations for topical formulations in stability-study design, data interpretation, and setting specifications in relation to IND and NDA submissions
- Analytical Methodology—Examine analytical methodology and illustrative examples for prototype formulation selection, method development/validation, including topical biopolymer formulations
- Safety Studies—Discuss aspects of CMC analytical support for non-clinical and clinical topical drug product studies

Who Should Attend:

- CEOs
- Presidents
- Managing directors
- Vice-president of R&D
- Vice-president of product development
- Vice-president of outsourcing and/or external development and manufacturing
- Chief scientific officer
- Chief scientist
- Chief technology officer

Presenters:

Simon Yeh, PhD,
Director of Analytical Sciences,
Dow Pharmaceutical Sciences

Moderator:

Patricia Van Arnum,
Executive Editor,
Pharmaceutical Technology and
Pharmaceutical Technology Europe

Presented by

Pharmaceutical Technology

Sponsored by

Dow Pharmaceutical Sciences, Inc.
The D in Topicals R&D
Since 1977

For questions contact Sara Barschdorf at sbarschdorf@advanstar.com

OUTSOURCING & CONSULTING SERVICES

Lyophilization

DSM offers a lyophilization system with the precision to serve demanding cycles. DSM's lyophilizers are equipped with LyoAdvantage software for cycle control, which provides the accuracy necessary for high-value products. The system enables scale-up from an 8-ft² unit that does not comply with good manufacturing practice to any commercial unit. **DSM Pharmaceuticals,** *Greenville, NC • www.dsmpharmaceuticals.com • tel. 252.707.4376*

Contract services

Metrics is a respected contract pharmaceutical research, formulation, development, and manufacturing company. Offering first-in-man (FTIM) development and Phase I–III clinical-trial materials (CTM), Metrics has conducted more than 120 FTIM studies for various chemical entities in the past five years while producing more than 700 batches of CTM. **Metrics,** *Greenville, NC • www.metricsinc.com • tel. 252.752.3800*

Contract services

Patheon is a leading provider of contract development and manufacturing services to the global pharmaceutical industry. The company supplies products and services to approximately 300 of the world's leading pharmaceutical and biotechnical companies. Patheon's fully integrated worldwide network helps ensure that customer products can be launched anywhere in the world. **Patheon,** *Research Triangle Park, NC • www.patheon.com • tel. 905.821.4001*

OUTSOURCING & CONSULTING SERVICES

Job-focused training

PDA's Training and Research Institute provides intensive, job-focused training that clients can apply immediately. The curriculum is designed to foster professional development in areas such as aseptic processing, biotechnology, environmental monitoring, filtration, microbiology, quality, regulatory affairs, training, and validation. Courses can be customized and provided at the client's location. **Parenteral Drug Association,** *Bethesda, MD • www.pda.org • tel. 301.656.5900*

Drug-delivery solutions

For more than 50 years, companies have looked to 3M Drug Delivery Systems for solutions to help their products meet the market's needs. 3M offers inhalation and transdermal drug-delivery systems and components, including dry-powder inhaler and microneedle technologies, plus state-of-the-art contract manufacturing services to help ensure technical success. **3M Drug Delivery Systems,** *St. Paul, MN • www.3m.com • tel. 800.643.8086*

Controlled packaging environment

Ropack, a leader in innovative packaging for the pharmaceutical and nutraceutical industries, provides a controlled production environment for blister, cold-form, and stick packaging. The Class 100,000 dedicated manufacturing suites deliver low relative humidity (approximately 20%) and low residual oxygen (< 2%) in a temperature-controlled environment. **Ropack,** *Montréal, Canada • www.ropack.com • tel. 888.353.7090*

OUTSOURCING & CONSULTING SERVICES

Crystallization services

Cambridge Major Laboratories's Netherlands-based Center of Excellence for Crystallization and Solid State Chemistry offers crystallization to obtain stable solids for purification or isolation. Additional services include: material characterization, solubility determination for production solvents and buffer solutions, salt selection, and crystallization process development to combine optimal synthesis conditions with and crystal-habit optimization. **Cambridge Major Laboratories,** *Germantown, WI • www.c-mlabs.com • tel. 262.251.5044*

Dosage-form services

Capsugel specializes in dosage forms and solutions for the healthcare industry. Its portfolio of products and services include: two-piece hard gelatin, liquid-filled, and vegetarian capsules, R&D equipment, and liquid formulations as part of its Licaps drug-delivery system. Capsugel also provides support to customers from formulation to final production. **Capsugel,** *Greenwood, SC • www.capsugel.com • tel. 888.783.6361*

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*

CLEANROOM EQUIPMENT & SUPPLIES

Sterile wipes

Veltek offers sodium-hypochlorite and hydrogen-peroxide wipes that are Class 10 laundered, filtered at 0.2 μm, and formulated with *US Pharmacopeia* water for injection. The products have laser-cut edges and are guaranteed to be sterile with lot-specific documentation. **Veltek,** *Malvern, PA • www.sterile.com • tel. 610.644.8335*

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*

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*

LABORATORY EQUIPMENT & SUPPLIES

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*

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*

Metal-detection systems

CEIA's THS/PH21N metal-detection systems feature high detection sensitivity for contaminating ferrous, nonferrous, and stainless-steel metals, even when the metals are present in small quantities. When contamination is detected, the system rejects the identified material. The system's failsafe operation monitors the opening and closing of the ejection flap through a redundant conformation sensor. **CEIA USA,** *Twinsburg, OH • www.ceia-usa.com • tel. 888.532.CEIA*

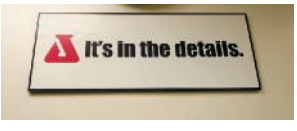
CHEMICALS, RAW MATERIALS, INTERMEDIATES, & EXCIPIENTS

Microcrystalline cellulose

The Ceolus KG-1000 product is Asahi Kasei's most highly compactible microcrystalline cellulose (MCC). Only a small amount (as little as 5–10% in some cases) in a formula will provide the desired tablet hardness. The company also offers the Ceolus KG-802 and UF-711 ingredients, and additional highly compactible MCC grades with different properties to solve various tablet-hardness problems. **AsahiKASEI America,** *New York, NY • www.ceolus.com • tel. 212.371.9900*

Formulation and process development

Evonik offers services in solubility enhancement of Biopharmaceutics Classification System Class II and III drug substances through melt extrusion and spray drying. Solid dispersions offer solutions for formulating poorly soluble drugs. The company's Melt Extrusion Modeling & Formulation Information System provides systematic screening of formulations and processing conditions at early stages of solid-dispersion product development. **Evonik Degussa Corp., Pharma Polymers,** *Piscataway, NJ • www.eudragit.com • tel. 732.981.5383*



Inorganic salts

Jost Chemical manufactures over 350 high-purity inorganic salts. The company's FDA-registered site in St. Louis, Missouri, totals 190,000 ft^2 and operates under bulk pharmaceutical cGMPs. Jost is a global supplier of chemical salts that meet USP/EP/BP/JP/ACS and multicompendia requirements. Jost's products are BSE/TSE free and allergen free, and its selection of products includes carbonates, nitrates, phosphates, and sulfates. **Jost Chemical,** *St. Louis, MO • www.jostchemical.com • tel. 314.428.4300*

CLEAN ROOM SUPPLIES

EQUIPMENT & SUPPLIES

OUTSOURCING RESOURCES

MANUFACTURING

OUTSOURCING

OUTSOURCED RESOURCES

CHEMICALS/EXCIPIENTS/API'S

Bulk Oils

LAB EQUIPMENT

Airflow Diagnostic Tools

MANUFACTURING/PROCESSING EQUIPMENT

Mixing/Blending/Drying

MANUFACTURING/PROCESSING EQUIPMENT

Used

OUTSOURCING RESOURCES

Analytical Testing

RECRUITMENT

contin. from page 98

Challenges ahead

Although the negotiated goals will go a long way in improving the safety of drugs in the supply chain, there were some disappointing aspects of the final plan. Industry associations hoped for faster implementation timelines than were identified in the FDA Performance Goals letter. For example, it is expected that inspection parity will increase confidence that drugs produced in foreign facilities are safe, but that goal is not expected to be met until 2017.

BPTF and EFCG also hoped for issuance of GMP certificates similar to those issued by European Union inspectorates. However, rather than issue these certificates, FDA will use an online database to indicate the inspection status of a facility. This database went online before approval or implementation of the GDUFA program and displays a site's status, if inspected in the calendar years 2009 and 2010. However, it is the BPTF's opinion that although the database is useful, providing that it is updated by the FDA in a timely manner (which is not currently the case), it will not be as useful to industry as a GMP certificate. In addition, it is unknown whether other regulatory agencies or drug-ingredient customers will accept this database status as an alternate to a formal GMP certificate.

The industry associations recognize the difficulty that FDA faces in bringing on personnel, appropriately training them, and getting systems in place to carry out GDUFA. Although not perfect, the Act is a big step forward in improving review timelines and parity of facility inspection.

The aims of GDUFA are important to American consumers, who can expect a safer and more efficient drug supply, and to the industry, which can expect a more level playing field. However, until the program is written into law, little progress will be made. While FDA indicates it will implement some review and inspection efficiencies immediately, many of the negotiated goals of GDUFA are several years away. BPTF and other organizations intend to work with Congressional representatives and their staff members to emphasize the importance of this initiative and encourage rapid evaluation and implementation.

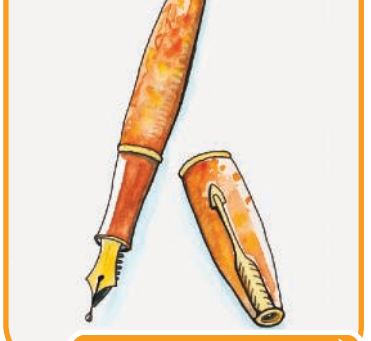
This work should build on previous interactions with Congress, including the Sept. 14, 2011, testimony before the US Senate Committee on Health, Education, Labor and Pensions (HELP) carried out by Deborah Autor, deputy commissioner for Global Regulatory Operations and Policy at FDA, and other leading industry representatives.

GDUFA is limited to generic drugs. Similar oversight of manufacturing sites making branded drugs and over-the-counter drugs is also needed, especially for those sites making APIs. It is hoped that the increased inspectional resources focused on foreign manufacturers under GDUFA will increase the inspection frequency and oversight of all foreign facilities. BPTF and EFCG encourage FDA to further collaborate with other countries with mature regulatory systems to recognize each other's inspections. Manufacturing sites often receive multiple inspections from different regulatory agencies focused on the same products and facilities. These duplicative efforts may be better spent inspecting sites with less mature regulatory agency oversight that may not have ever experienced a thorough regulatory audit.

In the near term, BPTF is pleased with the recent GDUFA initiatives and fully supports its promotion into law by Congress. Patient safety will be increased through increased application reviews, more frequent inspection of foreign facilities, and speedier access to safe and effective generic medicines. **PT**

Ad Index

Generic Drug User Fees Mark a Step in the Right Direction



DORLING KINDERSLEY/GETTY IMAGES

PharmTech.com/view

Patty Benson

SOCMA's Bulk Pharmaceuticals Task Force outlines key goals and challenges for user-fee legislation.

The recent development of a proposed Generic Drug User Fee Act (GDUFA) is designed to improve FDA's oversight authority and resources to expedite the review process and better regulate the increasingly global drug-manufacturing industry.

For several years, the production of drugs has been shifting away from US manufacturing facilities. The impact of this manufacturing shift is not inconsequential and has led to concerns about the safety of these drug products.

With more than 80% of APIs coming into the United States from foreign facilities, concerns about the safety of these drugs has become paramount. Chief among these supply concerns is effective regulatory oversight. Such oversight includes adequate review of drug applications and regular inspection of all manufacturing facilities to ensure that GMPs are in place and being followed. Inadequate resources and programs within FDA to perform these activities is a threat to patient safety and to the competitiveness of compliant manufacturers. This is where GDUFA can start to make a difference.

Background

The Bulk Pharmaceuticals Task Force (BPTF), an affiliate of the Society of Chemical Manufacturers and Affiliates (SOCMA), and the European Fine Chemicals Group (EFCG), a sector group of the European Chemical Industry Council (CEFIC), have publicly expressed concerns over the risk to public health associated with drugs produced at substandard foreign facilities. For years, these industry groups have supported registration and foreign-inspection fees as a means for increasing revenues to FDA to support more foreign inspections. More recently, a 2008 US Government Accountability Office (GAO) report pointed out that in 2007, FDA inspected less than 8% of foreign establishments and estimated that, at that rate, it would take 13 years to inspect all such establishments. Further, GAO noted that FDA lacked complete and accurate information on foreign drug-manufacturing establishments; such information crucial to understanding the drug supply chain.

In 2011, FDA engaged BPTF, EFCG, and the Generic Pharmaceutical Association (GPhA) to negotiate a comprehensive Generic Drug User Fee program. The end result of the negotiations was GDUFA, which is waiting for action by the US Congress in the current legislative session.

A primary reason for proposing GDUFA was to improve approval times for abbreviated new drug applications (ANDAs), eliminate the backlog of thousands of amendments and approvals, and ensure drugs (specifically, finished-dose and active ingredient) were being manufactured according to cGMPs. In 2011, the average ANDA approval time had slipped to more than 30 months with a backlog of more than 2000 applications; the backlog is increasing daily. Adequate FDA resources to provide effective reviews, as well as holdups due to inadequate or nonexistent inspections of production sites, contributed to these delays. BPTF, along with EFCG and GPhA, worked with FDA through a series of meetings to define performance goals, procedures, and funding to ensure a sustainable, effective program for generic drugs.

Key goals

As stated in the FDA letter published on the FDA website on Jan. 5, 2012, titled "Proposed Human Generic Drug Performance Goals and Procedures Fiscal Years 2013 through 2017," there are three primary aims of the GDUFA program: safety, access, and transparency.

Safety will be enhanced by ensuring that industry participants, foreign or domestic, who participate in the US generic-drug system are held to consistent high-quality standards and are inspected biennially, using a risk-based approach, with foreign and domestic parity.

Access will be enhanced by expediting the availability of low-cost, high-quality generic drugs by bringing greater predictability to the review times for abbreviated new drug applications, amendments and supplements, increasing predictability and timeliness in the review process.

Transparency will be enhanced by increasing FDA's ability to protect Americans in the complex global supply environment by requiring the identification of facilities involved in the manufacture of generic drugs and associated API as well as improving the FDA's communication and feedback with industry to expedite product access.

The improvements to safety and transparency are exactly what BPTF and EFCG have been advocating. All parties to the GDUFA negotiations indicated that they were willing to pay fees for inspections and filings to provide the necessary resources to ensure the FDA could meet the performance goals defined in GDUFA.

contin. on page 97

Your opinion matters.
To contribute to this column, send your proposal to adrakulich @advanstar.com.

Pharma&Biotech

Lonza

One step beyond

Reach beyond synthesis with Lonza's DuraSource™ life cycle extension services

Lonza's small molecules offering now extends one step beyond durable sourcing for mature, generic, and regionally important APIs. Get the benefits of 40 years of experience for the entire life cycle of your product.

- FDA approved facilities in Nansha, China and Visp, Switzerland
- Broad technology expertise to support 2nd generation processes
- Cost effective manufacturing setup in China
- Cost reductions year on year
- Continuous improvements through operations excellence and process R&D
- Global sourcing and material acquisition from cost leaders

Contact us at smallmolecules@lonza.com

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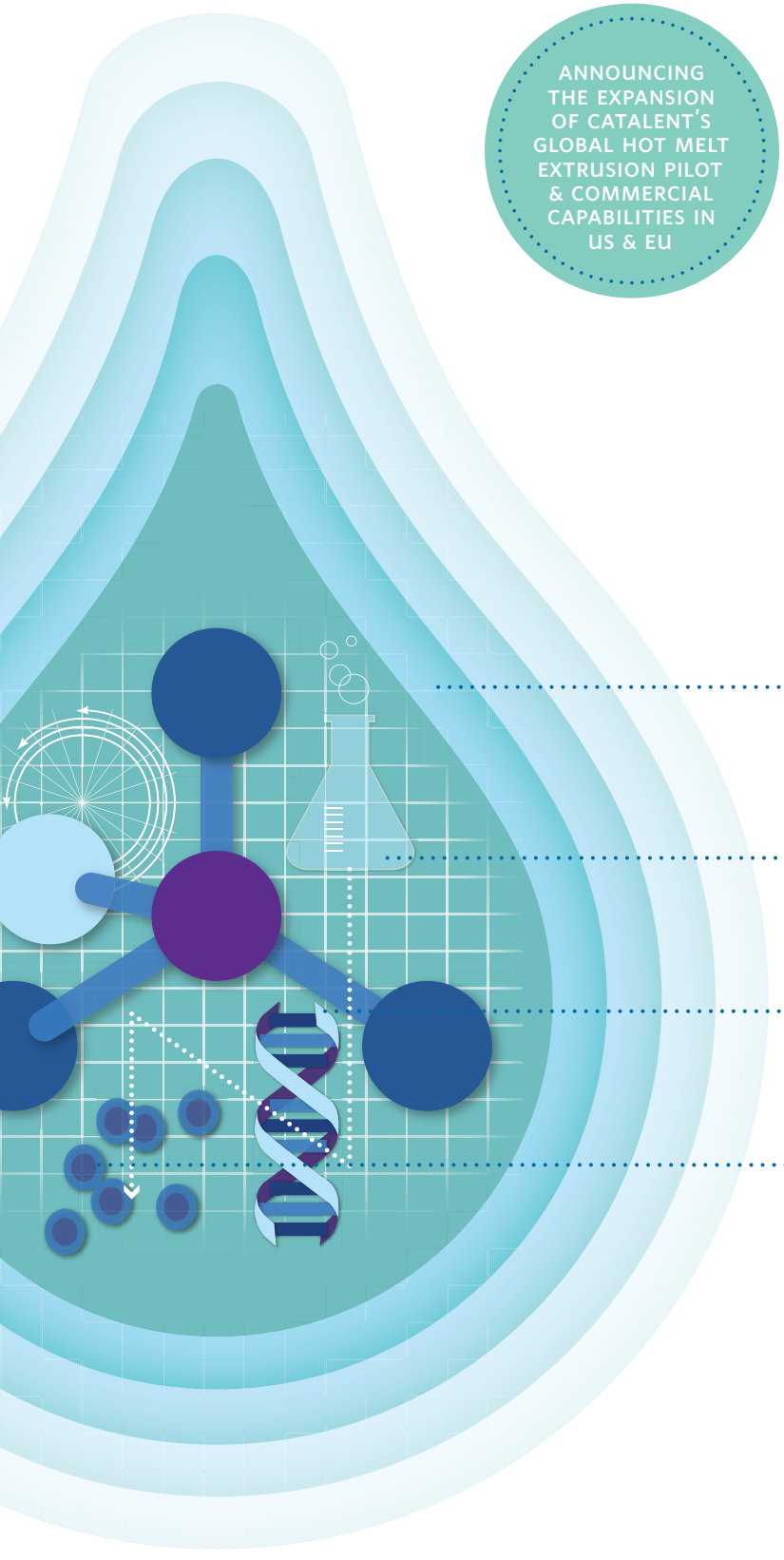
Catalent®

ANNOUNCING THE EXPANSION OF CATALENT'S GLOBAL HOT MELT EXTRUSION PILOT & COMMERCIAL CAPABILITIES IN US & EU



bioavailability solutions. **better treatments.**

With 1,000+ development and formulation scientists, Catalent has the talent, the expertise and the broadest range of technologies to solve the most complex bioavailability challenges. With proven success taking compounds from development to market globally, we can help you deliver more products and better treatments.

SOLVE WATER SOLUBILITY CHALLENGES

We help improve the performance of your poorly water soluble compounds with our innovative softgel delivery solutions, hot melt extrusion (HME) capabilities and Optiform® solid form optimization technology.

OVERCOME PERMEABILITY CHALLENGES

With our formulation expertise, unique film coating technology and fill formulations, we help enhance the permeability of your BCS III/IV compounds.

DELIVER MORE APIs

Our innovative, non-gelatin Vegicaps® technology, which can handle a wider range of fills and higher melting points, can help bring more of your challenging APIs to market.

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Our expert formulation scientists can help deliver more drug where and when needed with our controlled release or Zydis® fast-dissolve technologies.

Every molecule has a challenge.
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