



GMPs

Small Changes, Big Effects in Biological Manufacturing

A European Union-mandated formulation change—intended to increase the safety of Johnson & Johnson's Eprex (injected erythropoietin)—appears to have caused a 10- to 20-fold increase in the incidence of a rare but serious complication among recipients of the drug. Recent reports describe the origin of the adverse reactions and the detective work that found and fixed the source of the problem.

In 1998, the EU directed Johnson & Johnson (J&J, New Brunswick, NJ, www.jnj.com) to stop using human serum albumin (HSA) as a stabilizer in Eprex, the recombinant erythropoietin (EPO, a red blood cell growth factor) sold outside the United States. Polysorbate 80 replaced HSA in the formulation.

Over the next six years, dialysis centers, first in France and then world-wide, began to notice an increased rate of a serious anemia—pure red-cell aplasia (PRCA)—among patients receiving Eprex. The initial reports included 13 patients (11 receiving Eprex and two receiving NeoRecormon, an erythropoietin beta marketed by Roche). Further investigation—reported in the 30 September *New England Journal of Medicine*¹ by a team of researchers from the Jesse Brown Veterans Affairs Medical Center (Chicago, IL), Northwestern University (Chicago, IL), Inserm (Paris), and several other institutions in the US and Western Europe—turned up 191 cases of PRCA with onset between January 1998 and April 2004: 175 associated with Eprex, 11 with NeoRecormon, and 5 with Epogen, the HSA-containing erythropoietin marketed by Amgen (Thousand Oaks, CA). Incidence of drug-associated PRCA was similar from region to region, so most of the cases appeared in the largest markets: France, Canada, the UK, and Spain. The researchers estimated exposure-adjusted

incidence of PRCA per 100,000 patient years as follows: Eprex without HSA, 18; Eprex with HSA, 6; NeoRecormon, 1; Epogen, 0.2.

J&J initiated a 100-person crash program to locate and correct the cause of the problem. At October's Biotech 2004 meeting in Philadelphia, Thomas S. Templeman, director of biotechnology development at J&J's Global Biologics Supply Chain, LLC, reported the results of that effort. The polysorbate 80, added to replace the human serum albumin, interacted with the uncoated rubber stoppers long used in single-use Eprex syringes. The stoppers leached small amounts of plasticizers into the drug solution. These leachates acted as an adjuvant, stimulating a very small percentage of patients to mount a strong immunoglobulin G

response to the recombinant human erythropoietin. These antibodies also attacked the body's own erythropoietin, effectively halting almost all signals for the bone marrow to make red blood cells. The result was PRCA, a severe anemia requiring transfusions.

In 2002, J&J switched to PTFE-coated rubber stoppers, which have halted the leaching problem and greatly reduced immune response. The company now cites its experience as a strong argument for requiring new clinical trials whenever a new process begins to produce even tried-and-true biologicals—as would be the case with producers of follow-on biologicals.

—Douglas McCormick

¹ C.L. Bennett *et al.* "Pure Red-Cell Aplasia and Epoetin Therapy." *N.Engl.J.Med.* 351, 1403–1408 (2004).

REGULATORY

FDA Publishes Final PAT Guidance

The Food and Drug Administration has published the final guidance on process analytical technology (PAT). The document, *Guidance for Industry: Process Analytical Technology—A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance*, was posted on the agency's Web site on 29 September (www.fda.gov/cder/guidance/6419fnl.htm) and announced in the *Federal Register* on 4 October.

The PAT guidance describes a regulatory framework designed to encourage improvement in pharmaceutical development, manufacturing, and quality assurance through innovation in product and process development, process analysis, and process control. Conventional pharmaceutical manufacturing generally relies on batch processing with off-line

laboratory testing of collected samples to evaluate quality. PAT involves systems for designing, analyzing, and controlling processing through timely measurements—in-line, on-line, or at-line—of critical quality attributes. The guidance also establishes a regulatory pathway for implementing this new approach with the aim of alleviating industry concern that such innovation will lead to a regulatory impasse.

The final PAT guidance was one of several documents issued at the end of September, marking the two-year anniversary of FDA's initiative, "CGMPs for the Twenty-First Century: A Risk-Based Approach" (see "Washington Report," page 28).

Although most of the changes to the guidance were minor rewordings and clar-

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ifications, a few substantive changes appeared. The most significant of these expanded the scope of the guidance to include the Center for Drug Evaluation and Research's Office of Biotechnology Products, which was created after the draft PAT guidance was issued.

Another important change was that the section on process understanding was moved forward to emphasize the guidance's focus. "The main emphasis of PAT is understanding and controlling the process, and not trying to find exotic technologies for doing so," says Ajaz Hussain, PhD, deputy director of FDA's Office of Pharmaceutical Science. "Novelty for the sake of novelty is not what we are looking for. A focus on technology or sensors, without really understanding what their role is, is a waste of time and actually increases cost."

The final PAT guidance also encourages the use of PAT in product development. "This should end the finger pointing," says Nancy Mathis, PhD, president and CEO of Mathis Instruments Ltd. (Fredericton, NB). "When I talk to people in the industry, the manufacturing people say, 'PAT has to be built in and come over in a tech transfer,' which ultimately points back to formulation. But the people in formulation say, 'PAT

is not my job. Look at the guidance. It says it's for manufacturing.' The final guidance clarifies that PAT is intended to be used *anywhere* it can provide value."

Colin Minchom, Canadian vice-president of pharmaceutical development services at Patheon Inc. (Mississauga, ON), agrees that the mention of pharmaceutical development is important, but emphasizes a different benefit. "By using PAT, you can create tools to speed up the development process," he says, because on-line tools can allow you to see the consequences of scientific decisions faster. "We see that as a distinct advantage."

Hussain stresses that PAT fits into a broader concept of quality systems, a position that the agency detailed in a white paper, "Innovation and Continuous Improvement in Pharmaceutical Manufacturing." Issued the same day as the PAT guidance, the white paper is a summary of learnings from the CGMP initiative and proposed next steps for moving to what the agency calls the "desired state" of pharmaceutical manufacturing.

"What people have to understand is that the paradigm has shifted," says Hussain. "The entire approach to process validation and specifications now must be viewed in the context of quality systems. And it is a way to continuous improve-

ment. In the current state, continuous improvement is not possible."

Stephen Closs, a senior pharmaceutical process development engineer at Patheon, sees this connection between PAT and quality systems. "The links to ICH guidances Q8 and Q9 offer opportunities for industry to develop quality into processes," he says, referring to the International Conference on Harmonization's Q8 guidance, *Pharmaceutical Development—Quality by Design*, and Q9, *Risk Management*. Hussain points out that the approach is now international. "ICH Q8 will bring all the principles of PAT within that framework of quality systems," he says. "So this is a harmonized approach coming forward."

Industry members also felt that some of the apparently minor editorial changes were significant. "Nowhere in the new document do they refer to a specific technology," says Mathis. "That's very positive. It embraces the concept that new technologies will come out and that a company shouldn't have to look to the guidance to see whether a particular technology is listed or not." Hussain agrees. "We have always maintained the position that we will not recommend a particular technology," he says. "It's up to companies to see what is applicable and appropriate for a given process or product."

Mathis, who is a member of ASTM's Committee E55 on the Pharmaceutical Application of PAT, noted that the definitions of *on-line*, *at-line*, and *in-line* now match those in the standard on terminology issued by ASTM in May. "That kind of harmonization is important so that people don't get confused," she says. The final guidance also makes direct reference to standards being established by committee E55.

The final guidance also removes almost all references to the application of PAT to specific processes such as blending, another change that Mathis likes. "It opens people's minds that PAT can be applied to other processes such as those taking place in a liquid mixing tank, a reactor vessel, or a fluid-bed dryer, for example," she says. "Before I think people were thinking too much about blending."

—Laura Bush

REGULATORY

Aseptic Processing Guidance Is Final

Also on 29 September, FDA published its final guidance, *Sterile Drug Products Produced by Aseptic Processing—Current Good Manufacturing Practice*. This completes the agency's effort to replace the 1987 industry guidance of the same title. FDA published a revised draft in September 2003, based in part on recommendations from an aseptic processing working group formed under the Product Quality Research Institute.

Major changes from the draft include the revision of the sterility testing section to clearly emphasize and reference US Pharmacopeial Sterility Test (71). Table 1,

which summarizes clean air classifications and recommended microbial action levels, has been modified to acknowledge that alternative action levels can be justified, depending on the method of analysis used. Clarifications also have been made regarding process simulations. In addition, the guidance recommends "building quality into products" and underscores the agency's "encouragement of alternative approaches and innovations to achieve increased sterility assurance."

—Laura Bush



PACKAGING

Accenture Releases Results of RFID Test Program

After two months of testing and a year of designing, Accenture (Chicago, IL, www.accenture.com) has released the results of its radio frequency identification (RFID) prototype program targeting the pharmaceutical supply chain. Working with nine companies, including Pfizer, CVS Pharmacy, and Johnson & Johnson, Accenture tracked nearly 13,500 pharmaceutical packages using Manhattan Associates' middleware; Matrics tags, readers and antennas; and Dell servers. "Accenture worked with pharmaceutical companies to pull together a proof of concept implementation of the use of RFID throughout the supply chain," says Greg Gilbert, director of RFID solutions at Manhattan Associates (Atlanta, GA, www.manh.com).

The program involved the tracking of 10 real products through 15 locations. Manufacturers were required to verify readability of the tags before applying them to the products, and then track them through the supply chain. According to a report released by Accenture, the project team was able to read 98.6% of the case tags. When units were inside a case, the team was able to read 96.8% of the unit tags."

Several different scenarios were run, including recalls and product security. Accenture also worked with the Food and Drug Administration's Anti-Counterfeiting Task Force to learn more about how RFID can be used to snag counterfeit and gray-market drugs before they get to the street.

"We demonstrated that you can indeed create an RFID-enabled supply chain,

and [build] a safe and secure environment in terms of track and trace of product at the item level—from the manufacturer to point of dispensing," says Jaime Hintlian, a partner in Accenture's health and life sciences practice.

Accenture concluded that even though the project reached all its stated objectives, "full-scale implementation on an industry-wide basis will be more complex than many believe, requiring more time than anticipated to refine issues unique to the pharmaceutical industry."

A second series of tests will begin early next year to gauge the business value of RFID within the pharmaceutical supply chain.

—George Koroneos

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STANDARDS

USP Scientific Conference Draws Crowd and Raises Questions

At the United States Pharmacopeia's first Annual Scientific Meeting, held in Iselin, New Jersey, from 27 to 29 September, seven topic tracks engaged the more than 350 attendees in thoughtful discussion about challenges they face in formulation, quality control, and regulatory filings.

Process analytical technology (PAT)

The questions of causal and correlation relationships, available tools, and the limits of current manufacturing systems, all were explored in the PAT track.

Causal links between processes and products.

The first PAT session addressed the question, Can causal links be established between process critical control parameters (PCCPs) and critical product attributes to predict product quality, and ultimately, *in vivo* performance? Attendees postulated that if a

drug manufacturer has a complete understanding of which PCCPs are primarily responsible for the variability of critical product attributes, then the manufacturer can control the quality of the final product.

Practical approaches. The second session explored PAT approaches used in other industries. Attendees realized they cannot answer the causality question explored in the first session if the tools required to measure critical product attributes in real or near-real time are not fully developed.

Although some of these tools have been used successfully in other industries for quite some time, many cautioned that the problems pertinent to each application are very specific and often significant. Also, as production scale increases, so do the challenges of implementing the on-line applications required to measure the appropri-

ate attributes. What is possible in theory leads to tangible manufacturing concerns.

Near-infrared (NIR) and chemometrics. Advances in NIR spectroscopy and the use of chemometrics were discussed in the third session. Understanding how NIR behaves in real time, how chemometric data are collected, and the algorithms used to manipulate those data can help extract new information about the process. Because process-critical attributes are highly specific, a new algorithm approach has been developed for transferring chemometric relationships from one analyzer to another to correct for measurement bias.

Statistical modeling. The final session, "Mathematics and Statistical Underpinnings of Process Manufacturing," focused on applying statistical modeling to PAT.

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Participants explored key issues related to component selection criteria, the false-negative/false-positive quandary, the use of chemometrics for diagnosing manufacturing problems, and outlier detection. Important questions raised included:

- How can you determine if an outlier result is actually caused by model bias?
- What are the regulatory implications of recalibrating or revalidating your model?
- Can the original assumptions made about variable selection or specifications be changed to modify a model under new process conditions?
- What approaches will be allowed to achieve continuous model evaluation and improvement?
- Which statistical method is best for a given application?

These questions indicate that PAT still has to overcome many hurdles before the industry as a whole is ready to embrace it.

A broad approach to PAT, encompassing a scientific rationale for designing and implementing a good manufacturing process, will have broad applicability and can give companies a regulatory advantage with FDA. The restrictive application of PAT as a system of on-line measurements and controls will likely only increase efficiencies for large-scale manufacturing. Such controls will not help manufacturers that have not taken measures to understand their processes better to establish tighter specifications to control their processes.

The USP's perspective on PAT is related to the USP's role. When the industry moves to innovative new technologies, the USP must incorporate them into the public standard to continue to ensure the quality of the resulting products.

—Gary Ritchie, *US Pharmacopeia*

Regulatory paths for new excipients

A topic of discussion on day one of the "Excipients and Pharmaceutical Waters" track of the USP conference is one that consistently challenges formulators: how do you identify new excipients without fear of rejection from the regulatory bodies? Because excipients are reviewed as part of a new drug application, no stand-alone excipient

review or approval process exists.

For researchers trying to demonstrate that a new excipient is safe, speaker Robert E. Osterberg, RPh, PhD, recommended the procedures outlined by Steinberg¹ and Osterberg² to expedite the regulatory review of a new excipient. The speaker also suggested that researchers continue to test excipients with active ingredients in clinical/nonclinical trials and consult the FDA and CDER excipients guidances.

The creation of a regulatory body to confirm the safety of excipients could be another solution, Osterberg noted. For example, the industry could develop a panel such as the Cosmetic, Toiletry, and Fragrance Association's Cosmetic Ingredient Review Expert Panel, an organization that confirms the safety of cosmetic ingredients. According to Osterberg, FDA already has called the panel "an important voluntary effort."

Although excipient specifications traditionally have been for small molecules, emerging drug therapies such as bacterial/viral vectors are expanding the boundaries of what we consider to be "excipients." As speaker Shireesh P. Apte, PhD, of Alcon Research Inc. pointed out, such moieties could be considered excipients because they have pharmacological activity that may not be independent of their excipient functionality. Thus, emerging excipients may require regulation based on their functionality and their chemistry.

—Kaylynn Chiarello

Applying chromatography standards

During the the first chromatography session, questions raised about how to establish system-suitability led to a broader question: How much can chromatographic conditions be adjusted without revalidating the analytical procedure? Participants also raised the questions of when system-suitability requirements should be defined and whether *USP* monographs should include typical chromatograms.

¹ M. Steinberg *et al.*, "A New Approach to the Safety Assessment of Pharmaceutical Excipients," *Regul. Toxicol. Pharmacol.* 24 (2 pt 1), 149–154 (1996).

² R.E. Osterberg and N.A. See, "Toxicity of Excipients: A Food and Drug Administration Perspective," *Intl. J. Toxicol.* 22 (5), 377–380 (2003).

The second session addressed HPLC column-classification systems. *USP-NF* monographs refer to general column categories, but not all brands in a category perform in the same way. Key questions were raised about how the classification approaches of the USP and the Product Quality Research Institute should be made available to the public, and who should be responsible for evaluating public comments about those systems. The discussion will help USP decide on an approach for improving the current categorization system.

—Margareth Marques, PhD,
US Pharmacopeia

USP approaches to microbiology

In the microbiology sessions, the sterilization and aseptic processing discussions emphasized USP efforts to incorporate global practices. For example, the expert committee plans to begin a joint effort with the European Pharmacopeia to develop an information chapter on moist heat validation.

Experience using rapid microbiological identification techniques were also discussed. Participants emphasized that user requirements and expectations should be defined clearly before purchasing a system.

—Thomas J. Berger, PhD, and
Ellen Tonn, *Hospira, Inc.*

Making USP–NF Work for You

The four sessions of this track were designed to educate the audience about USP activities and processes. The first session covered USP fundamentals. Topics ranged from the value of setting standards for monographs and reference standards to the legalities of the *USP–NF*. The second session focused on how industry can effectively use the information in the compendia.

The last two sessions focused on the practical applications of the *USP*. The dissolution session discussed trouble-shooting apparatus, proper de-aeration techniques, and dissolution method development. Speakers also presented the new approach USP is considering of including multiple impurity tests in a single monograph. With this approach, users would determine the appropriate test method based on their knowledge of the manufacturing process used.

—Susan J. Schniepp, *Hospira, Inc.*



MANUFACTURING

Picking Sides: Catalytic Process Improves Drug Formulations

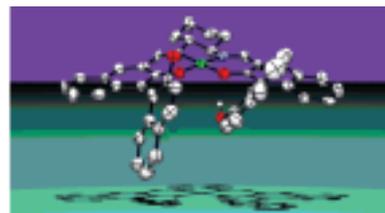
Distinguishing between the left- and right-handed versions of manufactured compounds is a long-established problem for drug formulators. Although they are mirror images, the two versions frequently react differently in the body (e.g., one side being therapeutic and the other causing harmful side effects). Because it's difficult to make purely left- or right-handed drugs, scientists at the University of Pennsylvania (Penn, Philadelphia, PA, www.upenn.edu) have developed a technique that forces precursors to choose a side to generate just one version of a drug molecule.

Penn researchers bind a single-enantiomer catalyst to a precursor, which makes the two sides nonequivalent and distinguishable. Typically, the catalyst blocks one side of the molecule so that the reagents can only approach from the other side. Activation of the coupling center is not necessary.

To select a compound to bind to the substrate, the Penn team uses a computational

program to design new catalyst candidates. Testing of the initial candidates generates empirical data, which is used to refine results and increase selectivity. "If the differentiation is just slight, we won't see selectivity," says Marisa C. Kozlowski, PhD, Penn associate professor of chemistry. "If it's large, we will see selectivity."

According to Kozlowski, the catalyst technique could offer significant advantages over other emerging chiral separation techniques. These approaches use a chromatography column packed with a chiral material to separate the compounds quickly. "The material in the column can be expensive," she points out. "In the long run, I believe our approach will be more cost effective." In addition, the catalytic process is more efficient because half as much of the compound is generated during the synthesis, she says. "You don't have to discard the other half of the compound after the separation," says Kozlowski. She notes, however, that



A chiral catalyst developed by the University of Pennsylvania.

each method has its own applications and advantages such as quick separation for the chromatography approach and efficiency for the catalysis process.

Because Penn's technology is unpatented and uses simple reactions and catalysts that most scientists can produce, their compounds can already be applied in formulations. At present, the group is working to expand its library of known catalysts because each precursor-end-product combination requires a different catalyst. Says Kozlowski, "No one catalyst can solve every problem."

—Kaylynn Chiarello

FORMULATION

Inconsistent Dosing from Splitting Tablets

A study investigating the appropriateness of pill splitting shows that those who divide a 10-mg tablet of the muscle relaxant cyclobenzaprine hydrochloride (HCl) to achieve a 5-mg dose may get anywhere from half to one-and-a-half times the intended amount of medicine. Splitting pills may result in either depriving patients of the medicine's benefit or exposing them to unwanted side effects such as drowsiness. Because patients would have no guarantee of consistently receiving the intended amount of medication, generic cyclobenzaprine HCl 10-mg tablets should not be cut in half. The findings appear in a recent issue of the *Journal of the American Pharmacists Association* (www.aphanet.org).

—Megyn Bates

FILTRATION

Prion Removal Filter Technology Inc. 2004

Because of the recent occurrences of variant Creutzfeldt-Jakob disease (vCJD, the human form of bovine spongiform encephalopathy, or mad cow disease) in the United Kingdom, Pall Corporation (East Hills, NY, www.pall.com) is investigating the transmission and control of the blood-borne prions (infectious protein agents) thought to be responsible.

The researchers are developing the "Leukotrap" affinity prion-reduction filter to remove both leukocytes and infectious prions from blood before transfusions. Research shows the new filter has an affinity for all types of prions including aggregated, denatured, and normal.

To validate the reduction of infectious prions, the researchers are studying the new filter using three different assays: Western blot assay, bioassay, and animal tests for transmission of scrapie (the

model for prion disease). They performed an endogenous infectivity study to determine the efficacy of a prototype filter in removing scrapie-infected prions from red blood cell concentrates. After a 300-day incubation period, none of the 20 hamsters that received the filtered red cells developed scrapie, whereas two of the 18 hamsters that had received unfiltered red cells developed the disease. Results showed that the filter removed infectious prions from red cell concentrates below the limit of detection of the Western blot assay; a bioassay showed that the filter removed approximately 4 logs of scrapie prions.

The researchers plan to move the new technology into operational trials in European blood-processing centers and hospitals in early 2005.

—Megyn Bates