

# DRUG GMP REPORT™

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## Industry Opposes FDA Suggestion to Review CMO SOPs

The drug industry is asking the FDA to rescind a recommendation included in recent guidance that drugmakers approve a contract manufacturing organization's (CMO) standard operating procedures (SOPs) and other protocols as part of a quality agreement.

In comments on the draft, issued in May (*DGR*, July), generic and brand drugmakers said following the agency's advice could cause confusion.

If other drugmakers use the same contractor, it could result in "numerous and possibly conflicting changes," Pfizer said.

It's not unusual for a CMO's SOPs to be used for multiple products and owned by a separate party, GPhA said. SOPs specifically

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## California Official Touts Perks Of ePedigree for OTC Drugmakers

While OTC drugmakers aren't required to serialize their products under California's electronic pedigree law, voluntary participation could benefit patient safety, officials charged with implementing the law say.

By January 2015, drugmakers must serialize 50 percent of their total product entering California's market. The remainder must be serialized by 2016. The track-and-trace law only applies to prescription drugs, but there are benefits to serializing OTC products, Virginia Herold, executive officer of California's Board of Pharmacy, said during *FDAnews'* pharmaceutical track-and-trace virtual conference last month.

"If the value for serialization is there for the prescription drug market, the OTC market will probably [want] a way to have the same kind of return on investment," she said. One such benefit is preventing drug

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## Long-Awaited ICH Draft Details Metal Impurity Controls

The International Conference on Harmonisation (ICH) released a draft guideline with tighter limits on metals in finished drug products, representing a drastic departure from the status quo.

The Q3D guideline sets permitted daily exposure (PDE) limits for certain metals based on safety and toxicology data.

Manufacturers currently abide by liberal impurity limits set by the U.S. Pharmacopeia, which are not strictly based on safety. And the screening method drugmakers use to gauge the presence of metals “[is] probably 100 years old,” Janeen Skutnik-Wilkinson, chair of the International Pharmaceutical Excipients Council (IPEC) Federation and a prior member of the ICH working group that developed the guideline, told *DGR*.

The guideline will “significantly change what people have done in the past because there are expectations for much lower levels.”

The guideline divides metals into certain classes based on toxicity:

- Class 1 metals include mercury, lead, cadmium and arsenic. These metals are significantly toxic across all routes of administration and typically have limited or no use in the manufacturing of pharmaceuticals;
- Class 2 metals include vanadium, molybdenum and cobalt — metals considered toxic to a greater or lesser extent based on how they are administered;
- Class 3 impurities have a relatively low toxicity if taken orally but require consideration in the risk assessment for other types of administration such as inhalation. Metals in this class include chromium, copper, tin and nickel; and
- Class 4 metals don’t have a PDE because their toxicity is very low. Such metals include sodium, manganese, calcium and zinc.

Skutnik-Wilkinson stresses that drugmakers should collaborate with excipient and active pharmaceutical ingredient makers to

communicate their expectations on impurity testing. A key concern is that some excipient makers say they test their products for heavy metals infrequently; in some cases testing only once a year (*DGR*, May 2012).

ICH is accepting comments on the guideline, and no deadline on the comment period has been set. Skutnik-Wilkinson said the goal is to finalize the guideline by next summer.

ICH’s *Guideline for Elemental Impurities Q3D* can be read at [www.fdanews.com/ext/files/08-6-13-ICHMetalGuideline.pdf](http://www.fdanews.com/ext/files/08-6-13-ICHMetalGuideline.pdf). — Robert King

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### CMO, from Page 1

required “for a product, or products, owned by the same owner should be reviewed and approved by the owner,” the trade group said.

Stakeholders also took umbrage with the definition of a drug’s “owner,” which the guidance states as “the party that introduces the drug into interstate commerce.”

The term could be misinterpreted as applying to the “distributor or promoter of another firm’s products,” said the International Society for Pharmaceutical Engineering.

Another drugmaker focused on an omission in the guidance: counterfeit drugs. Mylan recommended language that states if either the owner or contractor has any suspicion of counterfeiting, then it must inform the other party within 24 hours.

While FDA guidances aren’t legally binding, FDA officials have called for manufacturers to extensively examine potential suppliers before picking one.

Once a supplier is selected, the manufacturer needs to continually validate an array of technical and process information from that supplier, such as evaluation and acceptance criteria (*DGR*, September 2010).

The deadline for public comment on the draft, *Contract Manufacturing Arrangements for Drugs: Quality Agreements*, docket no. FDA-2013-D-0558, has closed. — Robert King

## FDA Issues Safety Alert For Texas Compounder's Products

The FDA is warning healthcare professionals that certain drugs from Texas-based Specialty Compounding could cause a bacterial bloodstream infection, becoming the latest safety incident to befall the scrutinized compounding industry.

The agency has received 15 adverse event reports from patients in two hospitals. The patients received an infusion of calcium gluconate two grams in Sodium Chloride 0.9 percent for injection and then came down with a bacterial bloodstream infection called *Rhodococcus equi*, reads an FDA notice.

“These infections are thought to be related to the infusions,” the FDA said. “Cultures from an intact sample of calcium gluconate compounded by Specialty Compounding show growth of bacteria that are consistent with *Rhodococcus* species.”

The company is recalling all of its sterile products, and emphasized that it has not yet confirmed the bacteria are linked to the medication, David Ball, a spokesman for Specialty Compounding, told *DGR*.

Ball added that he isn't aware of any deaths related to this incident.

The FDA said it is teaming up with the Centers for Disease Control and Prevention and Texas officials to investigate the cause of the infections.

Specialty Compounding received a Form 483 back in March. During an inspection that same month, investigators chided Specialty Compounding for lax gowning practices and a lack of established procedures that prevent the microbiological contamination of sterile drugs.

The inspection was part of a blitz performed by the FDA in the wake of a nationwide meningitis outbreak last fall linked to contaminated drugs mixed at a New England compounder. That outbreak, which has so far killed 63 and sickened more than 700, ignited a debate about how to properly oversee compounders, especially the larger ones.

The FDA has argued for more authority, while the compounding pharmacy lobby believes the states, which oversee traditional pharmacies,

can do the job. The Government Accountability Office agrees in a new report that the FDA needs clearer authority, giving reform proponents a boost (*see related story, page 7*).

Meanwhile, another safety issue has highlighted the limits to the FDA's authority over compounders. In an alert last month, the agency “reminds” physicians not to use questionable sterile products sold by Texas-based NuVision Pharmacy, which the FDA says has refused its request to issue a comprehensive recall.

The agency most recently issued a letter to NuVision July 26, citing poor compounding practices observed by FDA investigators during an April 2013 inspection of the company's Dallas facility.

Those practices raised concerns about a lack of sterility assurance of certain NuVision products.

The agency said it has received adverse event reports of fever, flu-like symptoms and soreness at the injection site associated with NuVision's methylcobalamin injection product that had been previously recalled. The FDA said it is not aware of any adverse event reports associated with other sterile products from NuVision.

NuVision responded to the letter by refusing the recall request, informing consumers on its website that state laws do not require compounding pharmacies to follow the agency's standards for manufacturing. NuVision is in compliance with USP 795 and 797, the pharmaceutical standards for compounders, it argues.

The full Senate is expected to consider a bill that adopts strict reforms for compounding pharmacies when it returns in September from its month-long August recess. The House Energy & Commerce Committee, meanwhile, has yet to take action on two bills which take very different actions against large compounders (*DGR*, August).

To read the Form 483, visit [www.fdanews.com/ext/files/08-9-13-SpecialtyCompounding483.pdf](http://www.fdanews.com/ext/files/08-9-13-SpecialtyCompounding483.pdf). — Robert King

## FDA Secure Supply Chain Pilot Finally Takes Flight

After four years and multiple false starts, the FDA is launching its voluntary Secure Supply Chain Pilot Program (SSCPP) designed to hasten the entry of imported drug products.

The agency published a *Federal Register* notice last month outlining the eligibility requirements for drug and active pharmaceutical ingredient makers to participate in the program. The pilot's goal is to increase the number of import entries that receive a "may proceed" designation from U.S. Customs and Border Protection (CBP), exempting the products from human entry review or examination.

The FDA said that participating in the SSCPP could increase the likelihood of receiving expedited entry.

To participate, a company must be highly compliant with FD&C Act regulations and

good manufacturing practices. Other requirements include:

- Having a plan in place for promptly correcting concerns the FDA might identify; and
- Having a validated Tier II or Tier III secure supply chain as defined by the CBP's Customs-Trade Partnership Against Terrorism, or C-TPAT, program.

The FDA will accept applications for the two-year pilot starting Sept. 16 through Dec. 31. The program will be limited to only 100 companies, with no more than five drug products per company.

The FDA first announced the program in January 2009. However, officials said implementation had been delayed due to issues with the Paperwork Reduction Act.

To read the *Federal Register* notice, visit [www.fdanews.com/ext/files/08-19-13-SupplyChainProgram.pdf](http://www.fdanews.com/ext/files/08-19-13-SupplyChainProgram.pdf). — Robert King

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## FORM 483 INSIDER

### Bayer Handed a Form 483 For Training, Lax Procedures

Inadequate GMP training and testing procedures landed pharma giant Bayer a Form 483 after an inspection of its Shawnee, Kan., facility.

During a May inspection, investigators found that the drugmaker's training program for titration does not "include proficiency and personnel qualifications," the agency said.

"In 2012 and 2013, there were at least two separate instances when the cause of an out-of-specification investigation was an untrained analyst or analyst not following procedure," reads the form, which contained six observations.

Both incidents were associated with the benzyl alcohol raw material assay by titration.

Bayer also lacks a procedure to "mitigate mix-ups of differing production data sheets," the agency said.

For example, an investigator saw batch record pages from five different products on an auditor's clipboard while in the packaging area for Precose (acarbose) 50 mg tablets.

Bayer responded that it submitted corrective actions to the FDA and "in response received an establishment inspection report from the agency indicating there are ... no further issues," spokeswoman Staci Gouveia told *DGR*.

To read the Form 483, visit [www.fdanews.com/ext/files/08-23-13-Bayer483.pdf](http://www.fdanews.com/ext/files/08-23-13-Bayer483.pdf).

### Teva Criticized by FDA Over Inadequate Batch Investigations

Teva Pharmaceuticals USA left FDA investigators wanting more focus on batch investigations and cleaning procedures, prompting a Form 483 for the generic drugmaker.

During a recent investigation of Teva's Sellersville, Pa., plant, agency investigators found issues with certain batch investigations.

Teva did not perform analytical testing of available reserve samples for five lots of drug products that were flagged for a lack of effectiveness, reads the six-observation form. The FDA also chided Teva for using a pump skid to make a batch of methylphenidate beads even though the skid was under quarantine after failing cleaning verification.

Teva was also cited for improper cleaning procedures. Drug residues were found on a "coffee grinder" used to grind up methylphenidate bead samples prior to moisture analysis. The problem is that the room and equipment underwent a major cleaning beforehand, the FDA said.

Teva said that it responded to the FDA's concerns and the agency told the drugmaker the response was satisfactory.

The Form 483 can be read at [www.fdanews.com/ext/files/08-23-13-Teva483.pdf](http://www.fdanews.com/ext/files/08-23-13-Teva483.pdf).

### West-Ward Investigations into Metal Contamination Don't Measure Up

West-Ward Pharmaceuticals has received a Form 483 for lax investigations into metal contaminants and batch deficiencies following an inspection of its Eatontown, N.J., plant.

Investigators found that West-Ward failed to identify all potential sources of metal contamination for lots of lisinopril and hydrochlorothiazide 20 mg/25 mg tablets, carisoprodol 350 mg, prednisone, USP 10 mg tablets and lisinopril 40 mg tablets.

The FDA was particularly dismayed because, "although all of these lots were recalled, the firm plans to resume manufacturing operations of these products."

West-Ward also did not conduct investigations into the confirmed presence of metal contamination in metal detector rejects, the form reads.

Investigators found that three lots of isosorbide mononitrate 30 mg tablets and one lot of

(See **Form 483 Insider**, Page 6)

## Ben Venue Ramping Down Production at Older Facilities

Ben Venue Laboratories is ceasing manufacturing activities at two older facilities in an effort to reorganize a company beset by quality problems over the past few years.

The Boehringer Ingelheim subsidiary revealed in a recently posted “update” that it will cease production at an older manufacturing plant and halt aseptic filling operations for drugs at its oldest facility by the end of the year.

The sterile injectable maker’s four manufacturing facilities are all located in Bedford, Ohio. The two facilities that are affected are the same ones that were temporarily shut down a few years ago due to quality issues, spokeswoman Marjorie Moeling told *DGR*.

Ben Venue said it will move production to “newer, more commercially sustainable facilities.”

“The decision to concentrate Ben Venue’s production in the company’s newer facilities will better position the company for long-term success,” Moeling said. The company will also trim down to about 800 people, but the “actual number of employees who will be displaced is yet to be determined,” she added.

The drugmaker has dealt with several quality issues over the past couple of years, including a recall for the chemotherapy drug leucovorin calcium after crystalline particulates were found in a small number of vials.

The company also received a Form 483 back in 2011 for failing to identify the reason that stainless steel particles wound up in two products it manufactured under contract. Ben Venue ceased all contract manufacturing at one of its Bedford plants after repeated good manufacturing practice issues (*DGR*, September 2011).

The drugmaker later stopped production altogether at certain Bedford facilities to address lingering equipment maintenance issues. The company restarted a handful of production lines last year to ensure enough supply of critically low drugs (*DGR*, November 2012).

The company is also currently under a consent decree to resolve manufacturing issues at Bedford. The decree required third-party facility assessments (*DGR*, February). — Robert King

### Form 483 Insider, from Page 5

60 mg tablets were rejected for “sticking and/or illegible logos attributed to the design of the tooling that caused air pockets between the tooling and the tablets during compression,” the form reads.

While the lots, manufactured between September and October 2012, were rejected, the investigation didn’t extend to other lots of the same drug that also had illegible logos and are currently on the market, the FDA said.

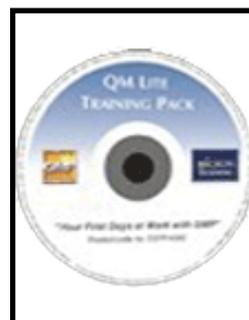
The drugmaker did not respond to a request for comment as of press time.

The Form 483 can be read at [www.fdanews.com/ext/files/08-23-13-West-Ward483.pdf](http://www.fdanews.com/ext/files/08-23-13-West-Ward483.pdf).

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## GAO Study Calls for Clearer FDA Authority Over Compounders

The Government Accountability Office (GAO) says in a new report that the FDA needs clearer authority over large compounding pharmacies, giving reform proponents a boost.

The GAO's report, prepared at the behest of the House Committee on Oversight and Government Reform, provides insight into the FDA's murky authority over compounders, the subject of an intensifying legislative battle on Capitol Hill.

Working from interviews with FDA officials and related stakeholders, the report echoes agency concerns that it doesn't have clear authority to inspect and oversee larger compounders that mix drugs without a prescription and distribute them to other states.

FDA officials told the GAO that it frequently gets challenged in court when it does try to inspect pharmacies.

"For example, from 2002 to 2012, FDA had to obtain 11 inspection warrants to gain access to drug compounders' facilities and records, representing nearly half of the 25 administrative warrants obtained by FDA for all FDA-regulated products in that same period," the GAO said.

Another point of contention is which pharmacies should be inspected by the FDA. The study notes that since compounders don't have to register with the agency, it can be a guessing game for the FDA and the state regulators that have primary watch over traditional pharmacies.

In a unique wrinkle, the GAO discovered that some compounders do register with the FDA as manufacturers for marketing purposes. However, the FDA doesn't necessarily inspect these compounders because they don't manufacture FDA-approved drugs.

Officials with the National Association of Boards of Pharmacy told GAO they knew of some compounders who eluded state oversight because they are registered with the agency and "the states assume FDA is overseeing these activities."

The GAO called on Congress to clarify the agency's authority over compounding

pharmacies, and wants the FDA to improve its inspection database to identify all of the agency's inspections of compounding pharmacies.

Proponents of congressional action noted that the study was "very helpful" to their cause.

"FDA has to know what facilities it is responsible for, and has to be able to hold them accountable to a quality standard," Allen Coukell, senior director of drugs and medical devices for Pew Health Group, told *DGR*.

(See **GAO**, Page 8)

## Fresenius Kabi on FDA's Radar Again with Fresh Warning

Drugmaker Fresenius Kabi has caught the FDA's attention again, this time receiving a warning letter for violations at its Maricao, Puerto Rico, blood bag manufacturing plant.

Fresenius said last month the warning stemmed from an April 2013 inspection of its subsidiary Fenwal, which Fresenius acquired in late 2012. The warning represents a new regulatory headache for the drugmaker, which has dealt with two recalls in the past few months due to glass particles.

Agency investigators took issue with the Maricao facility's "complaint-handling procedures, labeling ... and filing of field alerts not in accordance with FDA regulations," Fresenius said, declining to elaborate.

Fresenius stressed that the letter, issued Aug. 16, wasn't due to any adverse events.

The company said it has submitted a detailed remediation plan to the agency and that the plant has made "significant progress" in remedying the issues investigators raised.

Fresenius also had regulatory issues recently, recalling four lots of benzotropine mesylate injection, USP, 2 mg/2 ml (1 mg/1 ml) back in July. The drugmaker said that some vials of the Parkinson's drug may have contained glass particles. Fresenius recalled a lot of magnesium sulfate injection in May for the same reason (*DGR*, August).

Fresenius did not respond to a request for comment as of press time. — Robert King

**GAO, from Page 7**

Both chambers of Congress are considering compounding bills.

The full Senate is considering S. 959, the *Pharmaceutical Quality, Security, and Accountability Act*, which combines legislation to reform compounding pharmacies and establish a national track-and-trace system for pharmaceuticals (*DGR*, August).

The bill would create a new regulatory category for large compounding pharmacies, requiring them to register with the FDA, follow their own good manufacturing practices and report adverse events. The full Senate didn't consider it before adjourning for its month-long August recess.

Meanwhile, the House is considering two bills that offer drastically different visions for compound pharmacy reform. A bill from former Rep. Ed Markey (D-Mass.), the *Verifying Authority and Legality in Drug Compounding Act* (H.R. 2186), gives the FDA sole authority over large compounding pharmacies (*DGR*, June). And legislation introduced by Rep. Morgan Griffith (R-Va.), the *Compounding Clarity Act*, doesn't create new regulations but does clarify the FDA's existing authority (*DGR*, July).

The House Energy & Commerce Committee hasn't announced any action on either bill.

To read the GAO report, visit [www.fdanews.com/ext/files/07-31-13-GAOCCompoundingStudy.pdf](http://www.fdanews.com/ext/files/07-31-13-GAOCCompoundingStudy.pdf). The latest version of S. 959 is available at [www.fdanews.com/ext/files/07-31-13-S959.pdf](http://www.fdanews.com/ext/files/07-31-13-S959.pdf).

— Robert King

**California, from Page 1**

diversion. Herold said that stronger protections for prescription drugs may cause counterfeiters to look at OTC drugs, emphasizing the need for serialization.

Herold also discussed the 50-percent thresholds, saying that since they are estimates, California regulators will understand if drugmakers are off a little.

**Update on Capitol Hill**

Gabrielle Cosel with Pew Charitable Trusts provided an update on congressional efforts to establish a nationwide track-and-trace system for pharmaceuticals. The issue has gained traction on Capitol Hill, but is far from the finish line, said Cosel, manager of Pew's drug safety project.

The full Senate is considering a bill that would require unit-level traceability within 10 years of enactment (*DGR*, August). The Senate has yet to vote on the bill, which also includes an overhaul of compounding pharmacy regulations.

Sen. Lamar Alexander (R-Tenn.) is vociferously pushing for a vote, saying last month that Congress needs to pass the dual-reform bill "as soon as it returns" from its August recess.

The House, meanwhile, passed a track-and-trace bill in June that doesn't mandate unit-level drug tracking, instead opting for the FDA to issue a proposed regulation in 2027.

Cosel said that Senate and House staff have already met during the month-long recess to discuss the legislation and key differences between the bills. — Robert King

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