Drug Manufacturers, Distributors Not Committed to Unit-Level Tracking Plan

Drug manufacturers and distributors support efforts to establish a national track and trace system, but doubt that a unit-level pedigree system for drugs is feasible.

The industry’s sentiment is reflected in comments received in response to a new congressional track-and-trace proposal for a national-scale, unit-level pedigree system.

The comments on the proposal suggest that nothing has changed since industry and lawmakers failed to agree on track-and-trace language to be included in drug user fee bill approved earlier this year, Allan Coukell, director of medical programs at the Pew Health Group, said last month.

FDA Investigates Global Recall System as Part of International Pivot

SEATTLE — The FDA’s Office of International Programs (OIP) is exploring development of a single, global recall system that would encompass all domestic and international recalls.

The move toward a global system, currently in its early stages, would help address fast-growing gaps in global oversight of international product recalls, Mark Roh, regional food and drug director for the FDA’s Pacific Region, said.

The agency can no longer be “the quality control unit at the border that we have been for so long,” he said. Under the global approach being considered, the FDA and its foreign counterparts would jointly determine which country will take the lead in working with a company on a given recall, and the recall would extend to all countries.

(See Track and Trace, Page 2)
The latest proposal is in new legislation floated by House and Senate lawmakers, still in draft form, that would implement track and trace in two phases, with unit-level serialization and lot-level tracking taking place first and unit-level tracking and authentication following at a later unspecified time (DGR, November).

Pharma wholesale distributors say unit-level tracking is a future goal, contingent on the success of an initial lot-level system being implemented as a first phase.

Both industry and regulators prefer a national system over a patchwork of state laws. And wholesale drug distributors said they are not opposed to eventually moving toward a unit-level pedigree. However, they are generally disinclined to comment on the new proposal’s second phase because they believe laying the groundwork for a lot-level system will be daunting enough — and prohibitively expensive for many companies.

**Distributor Demur**

The infrastructure and processes necessary for widespread implementation of lot-based pedigrees are not currently in place in the pharma supply chain and would take years to establish, the Healthcare Distribution Management Association (HDMA) said in comments on the draft plan. Moreover, no standards currently exist for lot numbering structure or encoding a machine-readable lot number on individual units, the group added.

The HDMA, which represents the primary distributors that buy directly from drugmakers, calls for additional language allowing for the use of an “initial purchase transaction statement” on invoices to customers informing them that the products came to them directly from drugmakers. That system is currently in effect in Florida’s state drug tracking system, which allows the statement to be used by HDMA members, but requires more detailed pedigree processes of other distributors.

PhRMA commented on the draft through the Pharmaceutical Distribution Security Alliance (PDSA), crafters of the language that failed to win inclusion in the user-fee bill. The PDSA, which also includes HDMA, declined requests to share its views on the latest proposal.

Pew, the Washington, D.C.-based think tank that advises Congress on healthcare and user fee issues, calls for a strong electronic track-and-trace system similar to California’s ePedigree law. That law, set to take effect in 2015, speeds a path toward unit-level traceability and authentication using standardized numerical identifiers on product packaging (DGR, September).

Pew, in its comments, recommended the new congressional proposal include a concrete and swift path leading to unit-level pedigree.
— Johnathan Rickman

**Warning Letter Prompts Hikma to Halt Production at NJ Generics Plant**

Hikma Pharmaceuticals will cease commercial production at its Eatontown, N.J., plant through mid-January to focus on bringing the facility back into compliance with GMP regulations following a February 2012 warning letter.

Further, FDA observations from a recent inspection showed additional compliance work is required and halting production will allow it to be completed faster, Hikma said. The company could not be reached for additional information on the planned compliance fixes.

The remediation and additional restructuring for its generics business are expected to cost about $5 million this year, the company said.

The Eatontown plant’s shutdown was prompted by a June 2011 Form 483 and a February 2012 warning to Hikma’s West-Ward Pharmaceuticals subsidiary (DGR, October 2011).

The FDA said a possible “fundamental flaw” in controlled procedures at the plant may be contributing to significant variability in the thickness and hardness of in-process and finished drugs. And standard operating procedures allowed for release of product batches with significant in-process quality defects, the warning letter states. — Sarah Karlin
Hamburg Asks House for Legislative Fix of FDA’s Compounding Oversight

Republican House members are faulting FDA Commissioner Margaret Hamburg and the agency for failing to prevent a fungal meningitis outbreak tied to compounded drugs. But Hamburg, testifying at a subcommittee hearing last month, argued the FDA needs more authority to oversee compounding pharmacies.

Hamburg asked for legislation that would create a two-tiered, risk-based oversight system, with the FDA taking an oversight role for high-volume compounders and those dealing with the most complex drugs.

Under the commissioner’s proposal, compounding pharmacies would be categorized based on the following factors:

- Type of drug;
- Amount of drug being made;
- Whether the drug is being pre-made;
- Whether the drug will be shipped interstate; and
- Whether the drug is being dispensed to someone other than the ultimate user.

States would retain oversight of traditional, small-volume compounding pharmacies that produce customized medication for an individual patient in response to a patient-specific prescription.

For the higher-risk compounders, though, Hamburg asked Congress for new authority to collect and test samples of compounded drugs. The FDA also seeks clear statutory authority to examine records, such as prescriptions and volume data. And she requested funding to implement the proposal.

The Oversight and Investigations subcommittee hearing of the House Energy & Commerce Committee was called in response to the nationwide fungal meningitis outbreak linked to the New England Compounding Center (NECC) (DGR, November).

The commissioner said conflicting court cases have left the agency in limbo as to its current authority to regulate compounding pharmacies — a factor in its failure to prevent the outbreak. But Republican committee members argued that NECC was clearly operating as a manufacturer and the FDA had authority to take action.

“This was a complete and utter failure on the part of your agency,” said Rep. Cliff Stearns (R-Fla.), chairman of the subcommittee.

Rep. Henry Waxman (D-Calif.) encouraged the committee to try to get any new legislation passed in the current lame-duck session, which ends in mid-December. Rep. Ed Markey (D-Mass.) has introduced a bill that would force larger-volume compounders to register with the FDA as drug manufacturers. Those compounders would be subject to the same FDA inspection authority as drug manufacturers, according to the Verifying Authority and Legality in Drug Compounding Act.

However, Republican lawmakers complained that the FDA has not provided necessary emails and documents the committee has requested.

“If they want to go fast … they have to give us all the information they have internally,” said Rep. Michael Burgess (R-Texas). “If we just rush to legislate … we’re going to be back here with the same problem.”

Senators Not Persuaded

Senators pushed back against the agency’s proposed legislative fix, however, at a subsequent hearing of the Committee on Health, Education, Labor, & Pensions, calling it too complex. Committee Chair Tom Harkin (D-Iowa) and Ranking Member Michael Enzi (R-Wyo.) pointed to FDA failures to take enforcement action in situations where the agency already has oversight. For example, a 2006 warning letter to NECC states the FDA has clear authority to regulate the type of large-scale manufacturing taking place at the facility.

Meanwhile the FDA plans to hold a meeting with representatives from all 50 states Dec. 19 to strengthen its relationships and facilitate discussions about new compounding authorities, Hamburg said. — Ferdous Al-Faruque, Sarah Karlin
Corporate Integrity Agreements Offer Roadmap for Compliance Best Practices

Drugmakers seeking to step up their compliance programs should use other pharma companies’ corporate integrity agreements (CIA) as a model, attorneys with HHS’ Office of the Inspector General recommend.

“Across the board, the CIAs we have with pharma companies are the most sophisticated and extensive CIAs that we have,” Greg Demske, chief counsel to the inspector general, told attendees at the Pharmaceutical Regulatory and Compliance Congress in Washington, D.C.

He encouraged regulatory professionals industrywide to spend more time thinking and talking about compliance and to integrate CIA recommendations into their plans where applicable.

Focus on Financial Fraud

A common focus of OIG investigations is financial incentives that may influence individual decisionmaking, Demske said. In a recent attempt to thwart bad behavior by executives, the OIG drew up a CIA with GlaxoSmithKline that allows the company to rescind bonuses paid to executives if the business units they are responsible for are found to have engaged in wrongdoing. Demske hailed the agreement as a model for industry.

The OIG is also moving more aggressively to block company officials involved in fraud schemes from participating in federal programs.

Newer medtech industry CIAs spend more time discussing interactions between a company and its government payers and the ways manufacturers can educate staff about compliance in these relationships, noted Mary Riordan, senior counsel in the Office of Counsel to the Inspector General.

In terms of enforcement issues, Riordan said the OIG is seeing complaints that delve into more complex issues than the broader off-label promotion problems of the past. “We’re looking at messages,” she said. “Are you encouraging the use of the drug in amounts or for patients other than indicated on the label? Are you comparing your product to another product?”

The OIG is also investigating more allegations of companies misleading the FDA during the approval process and suppressing failed clinical trials, Riordan said. She anticipates scrutiny of financial relationships between drugmakers and physicians will intensify once payments are made public under the Physician Payments Sunshine Act. — Elizabeth Orr

Global Recall, from Page 1

The evolution is critical to the safety of the supply of medicines in the U.S., Roh said, since U.S. imports of FDA-regulated products could triple by 2015. Roh spoke at the Regulatory Affairs Professionals Society’s 2012 conference.

The effort is also intended to bolster the FDA’s transformation into an explicitly international organization; it grew out of the agency’s 2011 supply chain initiative, designed to foster partnerships with key foreign counterparts (*DGR*, July 2011).

Establishing the new system will likely require revoking or rescinding existing recall procedures and replacing them with new guidance documents. New legislative authorities would also be required to enable use of third-party assistance in global recalls. As a first step, Roh said the OIP is assessing the agency’s own ability to manage the transformation of the recall system and whether all parts of the agency support the change. After that, the FDA would begin evaluating the mechanisms needed to begin working with foreign partners.

The FDA’s charge to OIP to explore these possibilities comes as the Office of Regulatory Affairs (ORA) is being restructured to keep up with increasingly global operations (*DGR*, November). OIP and ORA together make up the larger Office of Global Regulatory Operations and Policy. — Johnathan Rickman
Hospira’s Austin Plant Gets 483 for Inadequate Complaint Investigations

Hospira, still struggling to fix GMP issues at a number of its facilities, received a Form 483 for failure to adequately investigate complaints or file timely field alert reports (FAR) about particulates found in products at its Austin, Texas, plant.

After receiving a complaint about particulates found in four bags of sodium chloride injection, USP, Hospira’s lab confirmed that each contained a different contaminant, including polyester fibers, nylon material, cotton and nitrocellulose, the form states. The follow-up investigation failed to take into account every potential source of contamination, overlooking the cloths that personnel use to clean plant equipment, investigators with the FDA’s Dallas district office said.

Particulate Problems Persist

A complaint received Feb. 3, 2011, regarding a black particle in a bag of lactated Ringer’s injection, USP was not looked into by lab personnel until more than a year later and it remained open as of Aug. 24, according to the form. The particulate involved was stainless steel.

As of Aug. 1, the facility had on file 11 complaints that had been open for more than a year, investigators said. Company procedure calls for completing complaint investigations in 30 days.

The FDA also rapped Hospira for failure to file FARs as soon as significant chemical, physical or other changes in distributed drug products are discovered.

No such submission was made for a report of “big black things” floating in a bag of lactated Ringer’s injection, USP from another compromised lot of the drug. The report was received at Austin on July 5, 2011, but a complaint sample was not analyzed until June 22, 2012, the agency said. Hospira staff declined to file a FAR, citing the product’s expiration. However, the product expired Feb. 1, 2012, months after the complaint was received.

FDA investigators also made repeat observations regarding the plant’s lack of an adequate training program to help staff identify defects in materials and products (DGR, November 2011).

The company has fully responded to the Form 483 and is committed to ensuring it has robust quality systems that meet the agency’s expectations, Hospira spokesman Dan Rosenberg said.


API Repackager Linked to NECC Gets 483 for Procedural Shortfalls

Alaunus Pharmaceutical, a repackager of active pharmaceutical ingredients (API), received a Form 483 for deficiencies in its stability program and recordkeeping procedures.

FDA investigators said Alaunus’ stability program for repackaged fentanyl, morphine sulfate, methadone, hydromorphone and bupivacaine bulk APIs is deficient for the following reasons:

- Alaunus only placed the first lot of each API received in stability;
- Alaunus has not placed one lot of each API in stability for each calendar year in that the APIs were repackaged into containers; and
- The company’s stability testing program for bupivacaine missed deadlines and lacks data.

Alaunus also has not performed any testing to assure that containers for holding the individual APIs in bulk are not reactive, additive or absorptive, the form states.

The form reflects FDA investigators’ findings from three recent inspections of Alaunus’ Framingham, Mass., facility. The inspections are part of a federal probe into the recent fungal meningitis outbreak as the company shares common
management with New England Compounding Center (NECC), the compounding company linked to the outbreak (DGR, November).

Alaunus’ master production records also came under fire for failure to define all critical steps in the master record. The form cites one example of failure to document the required step of labeling outer bags — the additional layer of containment — of bulk APIs.

Further, Alaunus’ batch production records lack complete documentation indicating which operator adds the outer label to API bags, and verifications of critical repackaging operations are not always timely, investigators said.

Requests to the company for comment were not returned by press time.

Sterile drugmaker Ameridose, another of NECC’s sister companies, received a Form 483 earlier this month revealing numerous contamination and quality issues (see story, Page 8).

The form to Alaunus is available at www.fdanews.com/ext/files/11-21-12-Alaunus-483.pdf.

Poor Process Controls Spur 483 for Hercon Laboratories

Hercon Laboratories, a maker of transdermal nitroglycerin patches, produced multiple laminate and finished lots of the drug without replacing rusted solvent coater burners that it knew, or should have known, had the potential to contaminate the product, a Form 483 states.

The rusted burners were discovered by employees at Hercon’s Pennsylvania plant on Nov. 29, 2011, during a retrospective qualification of the solvent coater, according to FDA investigators. The equipment problem created the potential for rust to drizzle on exposed drugs as they pass through the oven, they added.

According to the company’s equipment use log, the burner nozzles were not replaced until Feb. 22, 2012, with interim corrective action consisting of vacuuming the nozzles’ insides to remove pieces of rust.

There was no testing or visual examination conducted for certain laminate lots produced after the validation lots but before the rusted burners were replaced, the July 23 form states. And there was no investigation to assess the adequacy of the vacuuming as a solution to the issue, it adds.

Requests to Hercon for comment were not returned by press time. The Form 483 is available at www.fdanews.com/ext/files/11-16-12-Hercon-Labs-483.pdf.

Canadian Drugmaker Warned For Vendor Qualification Lapses

The FDA has hit International Laboratories Canada with a warning letter for GMP violations related to supplier qualification and the company’s quality control unit.

A February inspection revealed the custom OTC products maker did not establish the reliability of its suppliers through validation test results at appropriate intervals. The company relies on suppliers’ certificates of analysis without conducting adequate vendor qualification or specific identity tests of incoming components, the letter states.

The Oct. 23 letter also cites International Laboratories for several shortcomings with its quality control unit (QCU). The company has not established SOPs describing the unit’s responsibilities and there is no QCU oversight for the review of finished products before release. Further, the company has not adequately trained employees in GMPs.

The agency requests a plan for training personnel in GMPs and changing management procedures.

International Laboratories also failed to include all the necessary information on products in its master production and control records.


— Zachary Brennan
Canadian Drugmaker Warned Needed to Deter Diversion: Official

The FDA needs enhanced authority over state-licensed wholesale drug distributors to plug gaps in its ability to deter drug diversion and counterfeits, an agency official says.

The FDA doesn’t even know how many wholesalers there are in the U.S. and therefore cannot ensure the integrity of the pharma supply chain, Gregg Goneconto, senior operations manager in the agency’s Office of Criminal Investigations, said. That’s an “extreme vulnerability” in the supply chain considering many U.S. wholesalers distribute foreign-made products, he added, speaking on his own behalf.

Goneconto, speaking at the PDA/FDA Pharmaceutical Supply Chain Conference in Bethesda, Md., expressed doubt about the effectiveness of dominant state oversight, likening shared state/federal policing of wholesalers to that of compounding pharmacies.

States Take the Lead

As with compounding pharmacies, states largely oversee wholesale drug distributors but existing law allows the FDA to inspect wholesalers’ facilities in certain circumstances.

That regulatory “gray area” should be fixed to boost the FDA’s presence throughout the supply chain, Goneconto said. A risk-based approach to enhanced enforcement of wholesalers would be the preferred approach, with an especially watchful eye on smaller companies being a foremost concern, he added. Smaller and secondary distributors are most at risk for drug diversion, which has gotten more sophisticated over the years.

At the very least, he said, the agency should move immediately to put wholesalers on notice that if they break the law they may face criminal liability and seizure of the products they distribute. Failure to issue pedigrees pursuant to the Prescription Drug Marketing Act of 1987 could warrant product seizures.

The agency has given similar warnings to makers and distributors of illegal dietary supplements.

While diversion has tapered off in recent years, crooks continue to divert lucrative high-priced drugs for black-market resale.

The licensing of drug distributors is an issue in the new bipartisan track-and-trace proposal floated last month by House and Senate lawmakers (DGR, November). Along with creating a national standard for drug pedigree and tracking, the draft proposes a national licensing requirement for drug distributors. Distributors would also have to notify the FDA about new licenses or any changes to existing licenses.

Requests for comment from the Healthcare Distribution Management Association, which represents the primary wholesalers that buy directly from drugmakers, were not returned by press time. — Johnathan Rickman

Teva Resolves 2009 Warning Letter for California Plant

Teva Pharmaceuticals has resolved a long-outstanding warning letter for its Irvine, Calif., plant, the company said on its third-quarters earnings call last month.

Upgrades to the building and systems, as well as to manufacturing and quality processes, led to the October resolution of the letter, CEO and President Jeremy Levin said. The facility’s focus continues to be on producing the life-saving drugs on the FDA’s drug shortage list.

The Irvine plant closed in December 2009 for more than a year following an FDA warning letter citing quality control issues. The closure cost Teva hundreds of millions of dollars before manufacturing resumed in April 2011.

Last year, the company said it expected the plant to be back in full operation this past May but it did not indicate whether this has occurred (DGR, December 2011). — Sarah Karlin
Form 483 Reveals Contamination, Quality Issues at Ameridose Facility

FDA inspectors found sterility, potency and monitoring failures during a recent inspection of Ameridose’s manufacturing facility, according to a Form 483.

Ameridose is a sister company of the New England Compounding Center, which is at the heart of a nationwide fungal meningitis outbreak that has killed more than 30 people (DGR, November).

During its Oct. 10 to Nov. 9 inspection, the FDA found Ameridose:

- Failed to investigate at least 53 instances of microbiological contamination noted during the sterility testing of injectable drugs;
- Did not identify preventive or corrective actions to halt future sterility failures;
- Allowed orange, brown and green residues, as well as water leaks, to be present in some of the hoods and areas where sterile drug products were being prepared;
- Did not remove insects and at least one bird from an area where sterile finished product is packaged and stored;
- Failed to properly classify life-threatening patient complaints as adverse events; and
- Did not investigate a trend of seven complaints regarding one product that all related to low potency or lack of an effect.

Eric Kastango, president and CEO of Clinical IQ, a consulting company that works with compounding pharmacies, said the Form 483 highlights the need for tougher oversight of the largest compounders. “It’s an absolute embarrassment,” he said. Drug manufacturers feel pressure to comply with GMPs because of FDA enforcement. Compounders, however, don’t feel that same pressure because the state pharmacy boards overseeing them “really don’t do the thorough inspections that are required.”

The form follows a recall of all of Ameridose’s unexpired products from late October. The company also agreed to stop all pharmacy and manufacturing operations at the facility on Oct. 10 under an agreement with the Massachusetts Board of Pharmacy.

Meanwhile, the FDA reported it is resolving some of the drug shortages caused by the problems at Ameridose. Initially, shortages of sodium bicarbonate, succinylcholine, atropine sulfate, bupivacaine hydrochloride, lidocaine hydrochloride and furosemide were linked to the troubled companies. Valerie Jensen, associate director of CDER’s drug shortage program, said last month that by working with other manufacturers the FDA had nearly resolved all the shortages, with the exception of sodium bicarbonate products.

Jensen, speaking at the PDA/FDA Pharmaceutical Supply Chain Conference in Bethesda, Md., said sodium bicarbonate must be imported to help address shortages of that product.

View the 15-observation Form 483 to Ameridose at www.fdanews.com/ext/files/11-14-Ameridose.pdf. — Zachary Brennan

FDA Import Holds: How to Win Releases and Fight Holds and Refusals

An FDA NEWS Publication

This year, as the FDA begins to implement its new computerized import-screening tool called PREDICT, drug- and devicemakers are warily anticipating how it will affect the entry of their products into the U.S. Now you can learn the ins and outs of how the new FDA processes will work, so you can be better prepared to pass through customs — without holds or inspection.

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New WHO Working Group to Focus On Substandard, Falsified Medicines

The World Health Organization (WHO) is beginning discussions on a new international working group to help stem the spread of substandard, spurious, falsely-labeled, falsified or counterfeit (SSFFC) drugs.

The three days of meetings that took place last month are the first to discuss setting up and appointing the new member state mechanism, or working group, of six regional coordinators. The group will address nine objectives, including:

- Strengthening national and regional capacities and tools to prevent, detect and control SSFFC medicines;
- Ensuring the integrity of the supply chain;
- Exchanging best practices and information on current and ongoing initiatives to combat the spread of SSFFC drugs;
- Strengthening regulatory capacity and quality control laboratories for developing countries; and
- Enhancing other international collaborations and promoting the surveillance and monitoring of such drugs.

The meetings seek to establish the working group’s scope, structure, work plan and funding mechanism. Member states’ national regulatory authorities are being asked to collect data and provide the WHO with validated reports on SSFFC incidents, according to a report released prior to the meeting in Buenos Aires, Argentina.

The adoption of a member state working group also would combine regional efforts and build off the WHO’s prequalification program, which helps to regulate essential medicines and provides technical support in developing countries. In the past two years, the program has prequalified 70 new drugs, which brings the total to 300 drugs manufactured in 25 countries. The program also has prequalified 21 active pharmaceutical ingredients, including 15 for antimalarials, and provided support for 13 manufacturers in Bangladesh, China, Kenya, Nigeria and Pakistan.

The new WHO working group would build off work from the United Nations’ Office on Drugs and Crime, which is currently drafting a fraudulent drug strategy expected in 2013.

Meanwhile, a number of academics and researchers are criticizing the closed-door WHO meetings for their lack of ambition and lowered expectations.

There has been “a complete and total stasis” on falsified medicines at the WHO and there is little chance that something concrete will come from these meetings, Amir Attaran, University of Ottawa, told DGR. Attaran is lead author of a commentary on international action on falsified medicines, recently published in the British Medical Journal.

The lack of any international consensus on how to go after falsified medicines crime is holding the world back, Attaran said, noting that there are “countries that drag their feet and India and Canada are among the worst.”

(See WHO, Page 12)

Group Seeks Mandatory, Periodic Inspections of API Manufacturers

A European industry group is calling for mandatory inspections of all active pharmaceutical ingredient (API) manufacturers worldwide to ensure the safety of drug supplies. The inspections would be divided among the more advanced authorities and aligned with the International Conference on Harmonisation’s Q7 standard.

The call for mandatory inspections comes as the European Commission’s new falsified medicines directive is set to take effect next month. The directive requires API manufacturers outside the EU to obtain written confirmation from regulators confirming their practices meet EU GMP standards. Foreign companies have six months from the date the directive takes effect to comply.

But in a position paper issued last month, the European Fine Chemicals Group (EFCG) argues the commission should go a step further and

(See API, Page 10)
require mandatory inspections via international mutual recognition agreements. The group’s objections to written confirmations are three-fold:

- They may come from foreign authorities with less-rigorous standards than those of the equivalent countries;
- They may be valid for an unlimited period of time or issued by an official in a provincial office, rather than the centralized authority in the country; and
- They aren’t checked for authenticity and are not controlled or registered at ports of entry into the EU.

Roughly 70 percent of all APIs consumed in the EU come from India and China. But many plants in those countries are unlikely to meet EU GMP standards for years to come, the EFCG said. Recent inspections of Chinese and Indian facilities by the European Directorate of Quality Medicines resulted in the suspension or withdrawal of European Pharmacopeia certificates for seven API makers.

The EFCG is also concerned about a possible shortage of European drugs that require components from noncompliant foreign countries. U.S. API manufacturers have voiced their own concerns that stockpiling of APIs by European drugmakers in advance of the falsified medicines directive could trigger shortages in this country as well. The FDA has yet to issue any policy on how it plans to deal with the EU directive (see story, Page 11).

But if the 33 inspection authorities from the EU, U.S., Australia, Japan, Switzerland, New Zealand and Canada inspected the nearly 860 API manufacturing sites worldwide once every three years, using the ICH’s Q7 standard, then only about eight sites would need to be inspected by each authority annually, the EFCG said. And if the inspection outcomes were shared, the cost for each authority — paid through industry fees — would be about US $100,000, the group added.

In March, the FDA and its EU and Australian counterparts developed a blueprint for joint GMP inspections of API plants. The document is based on the partners’ ongoing collaboration on API GMPs, as well as a recent increase in participating entities, including the World Health Organization (DGR, April). — Zachary Brennan

ICH to Issue Clarifying Q&A On Q7 Guideline on API GMPs

The International Conference on Harmonisation (ICH) is developing a question-and-answer guidance clarifying its Q7 standard on GMPs for active pharmaceutical ingredients (API).

ICH has laid out the following goals for the new Q&A to achieve, including:

- Clarify issues related to supply chain control, outsourcing, monitoring of impurity profiles, quality systems and expectations in manufacturing APIs for clinical trials;
- Expand on how Q7 is applied as part of a harmonized lifecycle approach to product quality in line with the Q10 model;
- Harmonize Q7 with related guidance under review by the international Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (PIC/S);
- Establish uniform regulatory inspectional expectations for API makers, eliminating expectations that exceed the intent of the standard; and
- Summarize the impact of subsequent ICH standards on Q7.

A Q7 update is also needed because regulatory authorities outside the three participating ICH regions — the EU, U.S. and Japan — are increasingly interested in the organization’s harmonized guidelines and have questions about GMP training, FDA officials say (DGR, September).

PIC/S, which has published a training program and Q&A guidance on Q7 for regulators and their global network of investigators, will support the ICH working group’s efforts, ICH said. — Johnathan Rickman
FDA Lacks Policy to Address EU Falsified Medicines Program: Expert

The FDA’s lack of a policy or guidance to help API manufacturers deal with a new European program is causing concern among manufacturers about lost sales and drug shortages in Europe, an expert says.

Under the European Commission’s falsified medicines directive, all non-EU API makers must obtain written confirmation from their local regulatory authority to verify that APIs were manufactured according to good manufacturing practice equivalent with that in the EU.

But the FDA has yet to issue any guidance on how it will deal with such written confirmation for U.S. manufacturers, and at least four companies have expressed serious concerns about how the FDA will handle the issue in the near term, John DiLoreto, executive director of the bulk pharmaceuticals task force of the Society of Chemical Manufacturers and Affiliates, told DGR.

The written confirmation from third-party regulators comes into effect at the end of the year, although the EU is allowing a six-month grace period — until July 2, 2013 — for foreign API manufacturers to comply.

DiLoreto said the FDA, which has no current policy on the issue, seems “very resistant” to the idea of issuing certificates. This could in part be due to the additional paperwork burden the requirement would impose, but for API manufacturers this is the “11th hour,” he said.

Meanwhile, European customers are telling U.S. manufacturers they may stockpile certain APIs, which could lead to shortages, DiLoreto said. He has written to FDA Commissioner Margaret Hamburg about the matter.

The FDA could file for an exemption from the certification requirement, but has yet to do so. Switzerland, Israel, Singapore, Brazil and Australia all have asked to be exempted, and their requests are under review by the European Commission. The FDA did not provide a comment by press time on how it plans to deal with the directive.


Consent Decree Looms Over Hospira as Negative Inspections Continue: Analyst

Hospira continues to remain at risk for a consent decree as negative manufacturing updates, additional Form 483 observations and product recalls pile up, one analyst says.

“Dramatic” quality improvement is likely needed to avoid a decree, RBC Capital Markets Analyst Shibani Malhotra said last month following Hospira’s quarter-three earnings call.

FDA inspections and interactions with the company increased in the third quarter, Hospira CEO Michael Ball said. And the FDA typically conducts more frequent inspections when building a case for consent decrees, Malhotra has noted in the past (DGR, June).

One of those inspections led to a new Form 483 this quarter with 19 observations for Hospira’s Austin, Texas, plant (see story, Page 5).

The company’s anti-infective facility in India was also handed a Form 483 with five observations, prompting Hospira to voluntarily stop production there in October. Halted production allowed the company to address observations related to aseptic practices and put operators through an extensive retraining and certification process. Production has now resumed, and the plant should be fully operational in a few weeks, Ball said.

Meanwhile, a full GMP inspection at the company’s McPherson, Kan., plant resulted in two Form 483 observations, Ball added.

As the drug-related inspections continue, Hospira has also struggled with device warning letters and recalls during the quarter.

The remediation efforts for both pharma and device segments are turning out to be more (See Hospira, Page 12)
And discussions about intellectual property and drug pricing issues are holding back any real reforms on reducing the number of falsified or substandard drugs, according to the commentary.

Attaran calls on the working group to focus its efforts on creating an international treaty to overcome problems securing the pharmaceutical supply chain and criminalizing the distribution of falsified medicines.

The treaty should deal with both falsified and substandard medicines in a way that connects the “‘positive’ regulatory agenda and the ‘negative’ criminal agenda.” Such a treaty could also raise new money to help developing countries build regulatory capacity, assure quality manufacturing and train healthcare workers.

But Attaran remains skeptical about the progress of the new working group, noting that it “still cannot agree how to define the various poor quality medicines, much less settle on any concrete actions.” Other problems include:

- Anticounterfeiting laws that in some areas, such as East Africa, protect commercial interests and pay little or no attention to protecting public health;
- A lack of information on the global scale of the falsified medicines problem; and
- A tendency to conflate quality of medicines with tangential concerns such as intellectual property rights.

— Zachary Brennan

— Sarah Karlin

expensive than the company anticipated, likely topping $375 million, Chief Financial Officer Thomas Werner said. Last quarter, the company estimated costs would range from $300 million to $375 million, but that estimate is likely too low as it has already incurred more than $300 million in remediation costs, he added.

Ball reiterated Hospira’s previous announcements that quality initiatives are proving more extensive and time-consuming than the company originally thought.

Hospira pushed back estimates of when it expects the FDA to re-inspect its beleaguered Rocky Mount, N.C., plant to the first or second quarter of 2013. The company previously said the inspection was expected in late 2012 or early 2013 (DGR, September).

But the company is making progress, Ball told investors. He pointed to the start of construction on a new state-of-the-art quality control lab and the installation of the first automated visual inspection machine at the Rocky Mount plant.

Hospira also has seen rising production and release levels. The company is continuing with its plan to modestly increase production levels through the end of the year to improve the supply of market-critical drugs. It will adjust levels as needed to ensure the ramped up production doesn’t impact compliance efforts.

— Sarah Karlin
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