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Supply chain

FDA asked to clarify when DSCSA applies to drugs made prior to law's effective dates

SILVER SPRING, MD— FDA should accept the legal interpretation of the **Pharmaceutical Distribution Security Alliance** – an umbrella group for major drug manufacturers, distributors and their trade groups – or else "it is going to be very problematic for our members," an attorney for the organization told FDA's Drug Supply Chain Security Act (DSCSA) implementation input workshop here Oct. 14.

PDSA includes trade groups such as the **Generic Pharmaceutical Assn.** (GPhA), the **Pharmaceutical Research & Manufacturers of America** (PhRMA), drug firms such as **Merck**, **Johnson & Johnson** and **Pfizer**, distributors **AmerisourceBergen** and **Cardinal** (not **McKesson**) and **Walgreens** and other drug store chains.

Special report: FDA input hearing on DSCSA implementation
By Ken Reid, Editor

Eric Marshall, Senior Director at Leavitt Partners law firm in DC and an advisor to the PDSA, testified that his group and members feel that the November 2017 and November 2018 DSCSA dates for serialization do not apply to drugs "packaged" beforehand.

"At this point, any guidance from FDA contradicting our position would be very problematic," he said. "So, flexibility from FDA on guidance will be very important."

He said PDSA members "are working diligently to meet the electronic exchange and serialization

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GPhA seeks two-year delay in saleable returns requirements of DSCSA; HDA seeks end to multitude of state rules

SILVER SPRING, MD—The **Generic Pharmaceutical Assn.** (GPhA) Oct. 14 asked FDA to either delay the saleable returns verification requirements of the Drug Supply Chain and Security Act from Nov. 27, 2017, to 2019, or exercise enforcement discretion, to give firms time to scale up their packaging lines and other equipment requirements. *See Returns, page 2*

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readiness may depend on the supply chain as our members are just a portion of the overall industry."

Marshall said FDA needs to be "prepared to get questions about exceptions for product identifiers." He also said "there are a limited number of solutions providers and equipment vendors. They are driven by U.S. and international requirements, but it's straining their capacity."

Examples he gave included firms that provide packaging line equipment, required to serialize drug packages, and software providers, whom he said "are maturing" to the DSCSA rules.

Marshall said many of the drug makers rely on contract manufacturers for packaging "and they have different clients they work for." He said DSCSA has "changed business relationships and many organizations are facing a moving target."

As for the 2019 saleable returns date, Marshall said industry "has been working on this with various pilot projects," notably the one being done by the **Healthcare Distribution Alliance** (HDA.) He urged FDA to have "common evaluation criteria" and publish the results of these pilots "and see where you find gaps in pilot activity."

The law mandates that FDA conduct at least one pilot on serialization.

The Center for Drugs' (CDER) Deputy Director of Compliance Ilisa Bernstein also said the agency has to conduct three more meetings with the public/industry under the law. Commenting on Marshall's testimony, she said, "It sounds like we need to make sure product is being moved and we can handle business transactions now, but for some of these other pilots we need to be more forward-looking to get there."

Mike Rose, vice president, supply chain visibility for Johnson & Johnson, said his company feels that DSCSA's Nov. 28, 2017, deadline refers to a "manufacturing date," not a distribution date. "So, anything made after that date should be serialized, and that means we will be shipping nonserialized products after that date if they were made beforehand. I am not saying that is right, but that is our interpretation."

But Rose said J&J is "on track and on budget for next November," despite the multitude of products it makes that have to be serialized. He said the company also is aligning the new labels with contract manufacturers J&J works with.

Detailing information from J&J's implementation efforts, Rose said the firm has seen some internal benefits, such as:

- Reduction of manual work and an increase in productivity
- More precise data available for investigations of deviations or complaints
- Increased efficiency in product issue resolution
- Improvements in label print quality
- Reduction in the amount of disposable material and waste

Specifically, he said J&J realized savings from better "accuracy and standardized labeling for error correction. Higher fidelity inventory accuracy and visibility. Reduced need for checks, counts, claims and credits."

He said J&J three years ago began outfitting its two U.S. distribution centers for track and trace in anticipation of November 2017. He said the firm did a white paper with AmerisourceBergen and is participating in the HDA pilot.

However, Rose outlined these challenges J&J is facing, such as initial reduced productivity, dealing with sterilization processes, global harmonization of labels and complications implementing serialization by each product line.

Rose said it would be helpful for verifying returns if there was "some cloud-based or industry solution to verify the serial number for drugs returned and intended for resale. We want that for internal purposes, but it's an industry need as well."

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In addition, at the public input session on DSCSA implementation at FDA headquarters here, manufacturers and distributors said there is a need to conduct pilots on various serialization and track and trace methods, and that there is a problem with India-based companies providing proper unique facility identifiers (UFIs) in their labels.

Industry, however, pointed out numerous advantages to the new law and serialization, including analyzing deviation reports for GMP deviation purposes.

Under the agency's implementation schedule, manufacturers must put a unique product identifier on certain prescription drug packages no later than Nov. 27, 2017 and repackagers no later than Nov. 27, 2018). The product identifier consists of: National Drug Code - Serial number - Lot Number - Expiration Date.

After products are serialized, the only drugs that can be bought and sold in the U.S. will be those encoded with product identifiers (unless grandfathered under section 582(a)(5)); repackagers (beginning Nov. 27, 2018;

wholesale distributors beginning Nov. 27, 2019; and dispensers as of Nov. 27, 2020.

Verification product at the package level, including the standardized numerical identifier (NDC and serial number) starts for manufacturers Nov. 27, 2017, repackagers Nov. 27, 2018; wholesale distributors Nov. 27, 2019; and dispensers starting Nov. 27, 2020. Enhanced product tracing by 2023 is to be done at the package level.

Mark Hendrickson, Director for Sciences and Regulatory Affairs, said in prepared testimony that GPhA "and others in the industry continue to be frustrated by the confusion at the state level with the preemption provisions in the law.

"Members of the supply chain have been vocal federally and at the state level to attempt to clarify and educate on the provisions that impact state activities," he said, adding: "One area of specific concern is the continuance of differences in definition of terms used in DSCSA and in some state laws, even with respect to identification of supply chain sector."

As companies are concentrating on installing line and data systems, Hendrickson said, "there are outstanding discussions around the impact of DSCSA on industry quality systems, classification of serial numbers and a complete understanding of how to manage the serial number data requiring additional industry alignment."

"Additionally, while we appreciate the ability for industry to interpret the law and allow industry to make business decisions, in some cases the lack of FDA guidance causes some concern. Without input from FDA, industry lacks the confidence on our path forward on a number of technical areas. One example is the various questions surrounding the grandfathering clause."

Hendrickson said that "readiness for 2017 and future requirements are not just reliant on internal resources and processes. GPhA and many others in the supply chain rely on outside equipment, software and service vendors to implement the technology around DSCSA and in daily manufacturing activities. Our members have been working closely with these outside vendors for years preparing and educating to ensure everyone is compliant with the law. Based on these efforts we are concerned that the timelines have put significant resource constraints on the limited pool of vendors."

He explained in an interview after the talk that pioneer/brand-name drug makers can afford to have lines dedicated to one drug, whereas generics firms have to devote their lines to several products, thus making it more difficult to implement systems to meet DSCSA muster.

To both facilitate this industry discussion as well as utilize a building block approach on 2023, GPhA requested that FDA "consider moving the 2019 saleable returns requirement back to the beginning of the unit tracing requirements in 2023 when sending and receiving unit data will be part of transaction information on all units, including salable returns according to the law. Alternately, FDA could exercise enforcement discretion with 2019 requirements. Discretion around the 2015 requirements ensured robust testing and implementation of the requirements while allowing product to continue to flow to patients safely and securely. "

Asked if FDA could move the date, FDA's Bernstein said "we will look into it." However, experts in the law said that the date is grounded in the law, and only Congress can change it, but they said FDA could exercise enforcement discretion.

For the **Healthcare Distribution Alliance** (HDA), the "lack of federal licensure regulations" has been distributors' main concerns, said Anita Ducca, Senior Vice President, Regulatory Affairs, who was joined by Brian Waldman, Partner in the Washington law firm Arent Fox, who serves as HDA's Outside Counsel. HDA represents primary pharmaceutical distributors

While HDA said Phase I of the DSCSA "has been going pretty well," there have been challenges so far for wholesale distributors in integrating data requirements into systems and processes and establishing the necessary connections between suppliers and customers.

She said the lack of FDA issuing rules has been "unexpectedly and unfortunately…diverting scarce resources away from getting ready for 2019 and 2023 requirements."

Under DSCSA, FDA is required to establish federal registration requirements for distributors.

Ducca added: "Without the federal regulations, we're seeing state inspectors and state boards developing different interpretations and requirements that are inconsistent with the DSCSA and with each other. And once the federal regulations do issue, states will have to go back and amend what they've just changed, creating additional stresses for the states' limited resources, as well.

"These differences and inconsistences are unnecessarily complicating wholesale distributors' ability to obtain appropriate state licenses and are potentially opening gaps in requirements that may leave products at risk, all of which the DSCSA's national uniformity and other provisions were supposed to stop. Your help, by issuing the state licensure regulations, would be greatly appreciated. "

As for the 2019 saleable returns requirement, HDA said this verification requirement "has the potential to be very burdensome for both manufacturers and wholesalers."

As a result, HDA has sponsored a pilot study with its manufacturer and wholesale distributor members to test different verification methods, which the group said has worked. It will present the data Nov. 9-11 at a Traceability Seminar in Washington (See article below).

Ducca said in testimony that her members and association are concerned about the specific date of Nov. 27, 2017, in terms of grandfathering.

According to the law, Ducca said "beginning Nov. 27, 2017, manufacturers must affix or imprint a unique product identifier to each drug package and homogenous case that the manufacturer intends to introduce in a transaction into commerce. This serialization requirement applies to repackagers on Nov. 27, 2018."

The 2023 enhanced traceability system in Section 582(g) of the Act then takes all this much further. She noted five issues:

1. First, starting in 2023, the product identifier must be included in the Transaction Identifier (TI) for every transaction.
2. Second, in every product transaction, authorized trading partners must provide and receive TI and transaction statements (TS) in a secure, interoperable, electronic manner. Each authorized trading partner must provide TI and TS to its customer, who, in turn, will provide its own TI and TS to its subsequent customer, in each case with the TI reflecting the current ownership and sale. Note that I mentioned the TI and TS, but not the third T – TH. The statute provides that the requirement to pass the Transaction History sunsets in 2023 and is no longer required. "Transaction Statement" is a specific DSCSA requirement, Ducca explained in a followup email (See sidebar).
3. Third, when appropriate, it will be possible for each trading partner to manually or electronically read the unique product identifier and relate that identifier to the TI for that product. This means a trading partner will be able to identify, by unique product identifier, information about the transaction in which it acquired the product, and the date of that transaction. If the purchasing trading partner sells the product, it also will be able to identify, by unique product identifier, when it sold the specific unit of product, and to whom.
4. Fourth, each trading partner must have systems and processes to be able to promptly respond with the TI and TS for a product when FDA or other officials request it in the event of a recall or during suspect and illegitimate product investigations.
5. Fifth, and last, each trading partner must have systems and processes necessary to facilitate gathering the information necessary to produce TI going back to the manufacturer in response

TS and SNI explained

TS is defined in section 581(27) of the law as follows:

1. The 'transaction statement' is a statement, in paper or electronic form, that the entity transferring ownership in a transaction—
2. (A) is authorized as required under the Drug Supply Chain Security Act;
3. (B) received the product from a person that is authorized as required under the Drug Supply Chain Security Act;
4. (C) received transaction information and a transaction statement from the prior owner of the product, as required under [§ 360eee-1];
5. (D) did not knowingly ship a suspect or illegitimate product;
6. (E) had systems and processes in place to comply with verification requirements under [§ 360eee-1];
7. (F) did not knowingly provide false transaction information; and
8. (G) did not knowingly alter the transaction history.

Thus, the TS is more or less a statement that the trading partner selling the product must provide to the buyer that they're in compliance and, to their knowledge, the product is genuine.

SNI stands for "Standardized Numerical Identifier." DSCSA requires drug manufacturers and repackagers to affix or imprint a "product identifier" on packages for covered prescription drugs.

- The ''product identifier'' includes, in both human-readable form and on a machine-readable data carrier, the ''standardized numerical identifier,'' plus the product's lot number, and expiration date.
- FDA has defined the SNI as consisting of the product's National Drug Code (NDC) and a serialized number that the manufacturer assigns.

In essence, it the SNI is the NDC plus manufacturer's assigned serial number.

FDA's guidance defining the SNI can be found here: http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM206075.pdf

Source: Anita Ducca, HDA

to certain requests. These requests can arise in two situations: in recalls and in suspect and illegitimate product investigations. This doesn't mean a trading partner must produce TI going back to the manufacturer – that's the statutory definition of TH, which sunsets in 2023. Section 582(g) says that a trading partner has to facilitate gathering the TI that will enable the entity it is facilitating – likely FDA or maybe a trading partner – to assemble the TI for each transaction going back to the manufacturer.

Ducca said "inference" is key to how her industry will comply.

"HDA believes that inference will be essential to accomplishing them," she explained. "Inference in this context is a business process in which a collection of individual products moves through the supply chain in an outer container such as a pallet or case, and less than 100% of product identifiers affixed to the individual units within that outer container are scanned and/or read."

For a wholesale distributor to infer the contents of sealed cases or other containers that they purchase from manufacturers, manufacturers will have to provide wholesale distributors with data that creates the unit-to-case relationship of product and serialized data – referred to as "aggregation." Moreover, manufacturers will not be alone in this, as wholesale distributors will also need to aggregate many of the shipments for their customers. Given that approximately 15 million products move to and from wholesale distributors each day, inference will be essential to allow wholesale distributors to move this volume of products. HDA strongly urges FDA to consider the need for inference and by default, aggregation.

"Facilitate gathering," a concept mentioned earlier, also merits additional exploration as it is another, and new, requirement designed to further secure the supply chain. Trading partners have always cooperated with one another and the Agency on recalls and investigative efforts, but the DSCSA now expressly requires them to provide even greater assistance to FDA (or other appropriate entity) in such investigations.

With the application of the unique identifier on all products transacted, trading partners gain both visibility into the identity of each individual unit and the ability to trace that unit. Distributors will be able to scan or otherwise look up a product's identifier and be able to give FDA or other regulatory authority exact information about the previous owner or subsequent purchaser for any product that they transacted. These identification and traceability capabilities to facilitate gathering a product's TI are achievable because of the product serialization made possible in the DSCSA.

Moreover, a complete profile of the products' ownership will be rapidly available because the vast majority of wholesale distributor purchases are direct purchase transactions. This means that only three entities would typically have a unit of product's TI – the manufacturer (or the manufacturer's exclusive distributor), the wholesale distributor and the dispenser.

She added: "We fully anticipate that the multiple additional security provisions that will have been put into place before 2023 will make instances where investigations into suspect or illegitimate products in the U.S. supply chain are very rare events. However, the additional trading partner capability that the DSCSA adds will clearly provide an important level of support for such investigations moving forward.

Uniquely identified, serialized product changing

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ownership in an electronic, interoperable system is also critically important to the verification the DSCSA also requires. Verification means determining whether the product identifier affixed to or imprinted on a package or homogeneous case corresponds to Standardized Numerical Identifier (SNI), which the manufacturer or repackager assigned to the product.

In the DSCSA there are two instances in which trading partners must verify that a product's identifier corresponds to the manufacturer or repackager's SNI: suspect product investigations and when a wholesale distributor wants to resell a customer return. "We emphasize that these are the only instances when wholesale distributors must verify a product's identifier," she explained.

Ducca said "the enhanced traceability for 2023 that we've described far exceeds what was required before the DSCSA was signed, and even what the DSCSA requires before 2023. In 2023, trading partners will have the ability to obtain critical transaction data about each unit of product purchased and sold based upon manually reading or electronically scanning each unit's unique identifier. Data will be shared in an electronic and interoperable format."

Ducca added that: "The advances of the 2023 enhanced traceability model should not be lost in the many details to move the industry to this new level of accountability. It should be recognized for what it is—a very significant enhancement in supply chain security that is far beyond where we were only a few years ago."

Confusion seen with GTIN, especially in India; industry requests 'guiderails' from FDA, not proscriptive guidance

SILVER SPRING, MD—There already is some confusion among drug companies, particularly in India, where DSCSA requirements conflict with India export labeling rules, particularly in the composition of the GS1 global trade item number (GTIN), industry told FDA at an input session on DSCSA implementation here Oct. 14.

Under DSCSA, a unique product identifier must be placed on certain prescription drug packages by manufacturers no later than Nov. 27, 2017, and no later than Nov. 27, 2018, for repackagers. The product identifier consists of the NDC code, serial number, lot number, expiry data and two-dimensional (2D) bar code.

However, slides were shown at the meeting indicating a lack of consistency on drug packages coming from India, where firms are trying to implement DSCSA requirements using the GTIN standard.

William Fletcher, managing partner of **Pharma Logic Solutions**, Yardley, PA, said Indian firms are using their country prefix (03) before the NDC code. He explained that GTIN "doesn't begin with 03, and does not know there is an NDC number in there. I think the emphasis has to be that the NDC code needs to be in the symbol and put it in the GTIN."

Scott Mooney, vice president, distribution operations for **McKesson**, La Crosse, WI, said "they're reading it slightly different over there."

In his presentation to the meeting, Mooney said "we find GTIN to be the biggest problem," saying the National Drug Code (NDC) should be in the GTIN and there "needs to be guidance on this."

He said a lot of products coming from India have labels "not converted to the NDC. Many other countries have different assignment numbers.

"There is a lot of confusion about the NDC being embedded in the GTIN. It comes from the fact you follow the standard of the NDC being in the bar code, but if you go online and figure out how to convert the NDC to the GTIN, you will find several [numbers] that come from the CBER [Center for Biologics] side, such as vaccines.

"I don't find a clear reference on the CDER [Center for Drugs] side that says, 'We are following the same conversion.' So, that is part of the confusion."

Mooney said GTIN is holding a workshop on this issue, "but it's something we need to get out to the industry."

Mooney also said McKesson has found "issues around encoding in data formats." He also said McKesson has found "problems with machine reading dates."

Mooney said his firm is going to start a project after January to scan 2D bar code data "and give our feedback to suppliers."

Heather Zink, of competing distributor **Amerisource Bergen**, said her firm participated in a returns pilot, but also did its own pilot last year to "understand the serialization process, test technical capabilities and measure the impact on operations, data and shipping errors" involving drug products. She said

four Amerisource distribution centers participated with four drug manufacturers.

The goal was to see "if we could get a serialized data file into our system."

She said the major "bumps" occurred with EPCIS data exchange and scanning. EPCIS stands for Electronic Product Code Information Services, which is a global GS1 Standard for creating and sharing visibility event data.

Zink said "not all labeling is equal" and "exceptions will be a challenge." Zink showed examples of how drug firms affixed labeling to their boxes in such a way that "the bar code was on the corner crease, and when you set the case up, there was 'bowing' so scanners could not capture the full information."

In one case, the manufacturer "put the shipping label over the bar code." Some labels were placed on "concaved surfaces."

Zink said her firm will do an "exceptions pilot" in 2017, this time with 12 manufacturers. The focus, she said, will be on "developing a process to resolve exceptions," such as packaging labeling issues and products with no data.

Rather than guidance, she said, FDA needs to provide "guiderails."

"Don't tell us exactly how, but we need guiderails – not telling us exactly how to do it."

"The sooner you get this to us before it impacts the registration dates, the better. We may need months and years of testing and communication with a trading partner," Zink said.

FDAers, however, said some things must be handled company to company.

Bernstein explained: "There's guidance and information that the agency can provide. We can put out strict standards and detailed information on 'how it should be done', at least from our perspective. But there are issues that have to be resolved trading partner to trading partner, so where is the happy medium?"

Zink said many drug makers want "global requirements and standards to bar code quality, GS1 for example." The **Healthcare Distribution Alliance** (HAD) also has barcode standards, as does the **International Standards Organization** (ISO.)

India: DSCSA and India export labeling rules conflict

Zink also said India has been a problem with "bar code confusion." (See next article)

"India doesn't know what to do," she said. "They are throwing every bar code on the planet." Zink showed slides with two different GTINs from India-based drug makers.

She explained that DSCSA requirements conflict with Indian government requirements for export serialization.

Dave Mason, associate director SPT supply chain program lead, **Sandoz**, Princeton, NJ, said his firm had to "negotiate with the government [India]" on labeling product made there for both DSCSA and India export labeling rules.

"It's a different law and has not had a lot of industry input," he said of India's export requirements. He said the country has a data base "they want us to put our products in, and we're very concerned about the security of serial numbers the way we have to report it to India."

Mason said the India rule "conflicts with GMPs," too. "It requires us to put in dummy pricing and pictures in their data base. We are very concerned about the security of serial numbers if we have to report it to India."

The **Generic Pharmaceutical Assn.'s** Hendrickson said in an interview that a major cause of the issue in India "is a lack of guidance" from their drug regulatory authorities, leading companies to have to "find out what to do through back channel resources."

Serialization

Nearly 50% of Indian pharma firms under pressure to opt out of U.S. market over DSCSA mandate

Even as the November 2017 deadline for implementation of second phase of the Drug Supply Chain Security Act (DSCSA) is approaching fast, approximately 50% of Indian pharma companies are under pressure to lose their U.S. market share due to their inadequacies to comply with pharmaceutical serialization regulation and traceability, **Pharmabiz.com** reported Oct. 25.

DSCSA is being implemented in three phases starting from Jan. 1, 2015, through Nov. 27, 2023.

Phase 1 is already effective since January last year and enforcement started from May 1, 2015. Manufacturers are accountable for product tracing, work

with authorized trading partners, verification (transaction information, [TI]) and transaction history (TH), authorized distribution of records (relating to the distribution of drug samples) and compliance with Uniform National Policy.

Phase 2 starts from Nov. 27, 2017, wherein manufacturers are accountable for product tracing, product identification, suspect product, requests for verification and saleable returns product. Manufacturers have to apply a new product identifier 2D datamatrix code on saleable packs of all of their prescription drugs in the first phase before Nov. 2017.

Product identifiers must contain standardized application identifiers (01) (17) (10) and (21), which uniquely identifier the GTIN, expiry date, batch number and serial number for each saleable pack. Two-dimensional (2D) Datamatrix shall carry both machine-readable data as well as human readable information, which is encoded in the 2D Datamatrix. From 2018, the same is applicable for repackagers, from 2019 it is applicable for wholesale distributors and from 2020 the same is applicable for dispensers in the as-mentioned sequence.

The DSCSA will have tremendous benefits in terms of consumer safety, protecting pharmaceuticals from fraud and counterfeiting and improving products' efficiency.

Serialization of saleable packs (bottles) to pallets of pharmaceuticals mandated by DSCSA will immensely affect the supply chain of pharma business. Indian companies exporting to the U.S. market will have to implement a slew of upgrades of existing lines and make additional investments into aggregation lines and reporting software to fulfill the DSCSA mandate. A number of companies do not have adequate space at manufacturing plants to put in place serialization systems. Approximately 50% of pharma manufacturing plants need to expand their packaging space to incorporate serialization and aggregation workstation units. The warehouses, logistics and distribution set-ups also carry out repackaging works and will need reaggregation units within these facilities, said Arjun Guha Thakurta, director-operations, **Life Science Consulting Pvt Ltd**, a **Conval Group** company.

A majority of Indian companies, faced with space crunches at manufacturing sites, are encountering hurdles to comply with serialization requirements at Level 3 (site level software and hardware. Master data such as customer, product and work order information are generally managed in this layer) and Level 4 (i.e, business logistics systems), said Thakurta.

They have so far put in place serialization at first and second line levels. Level 1 encompasses line level systems such as printers, scanners, cameras, code readers and controls. Level 2 denotes line level control systems consisting of software that controls data, serial number management. The software also aggregates data across all Level 1 devices on a specific packaging line, he said.

In order to make changes in the facility layout of the packaging area, the companies have to stop production, carry out civil work, replace HVAC systems, ensure requalification of the packaging hall and subsequently implement track and trace system. This will entail additional investment and loss of production.

In a bid to save on cost, most small and medium Indian companies are opting for local vendors over global suppliers which cost generally 30-40% higher than local supplier. Because local suppliers often lack knowledge of GxP data integrity and compliance mandates of U.S. FDA and EU, the Indian pharma company is very likely to fail in catering to the needs of the companies, he said.

Under the DSCSA mandate, manufacturers, repackers and wholesale distributors need to provide applicable TI, TH, and TS not later than one business day, not exceeding 48 hours after receiving the request for information from FDA or another appropriate federal or state official in the event of a recall, or for the purpose of investigating a suspect product.

Without putting in place effective serialization solutions from Levels 1-4, manufacturers will be unable to respond to the request of wholesalers and repackers within stipulated time, he concluded.

HDA's 2016 traceability seminar to discuss results of saleable drug returns pilot study, DSCSA implementation progress

The **Healthcare Distribution Alliance** (HDA), Arlington, VA, will host its annual Traceability Seminar Nov. 9–11, 2016, at the Renaissance Washington, D.C., Downtown Hotel, and discuss results of a pilot held with pharmaceutical firms regarding DSCSA implementation issues.

According to an association news release, the seminar will host supply chain leaders — including distributors, manufacturers, pharmacists and third-party logistics providers — as well as federal/state regulators to discuss upcoming milestones and lessons learned as they continue to implement the Drug Supply Chain Security Act (DSCSA).

Connie Jung, PhD, acting associate director for policy and communications, in the FDA Office of Drug Security, Integrity and Recalls, will deliver a keynote presentation on the DSCSA guidance the agency has provided, how FDA is preparing for the implementation milestones and the agency's expectations for the pharmaceutical supply chain as it steadily approaches the 2023 completion date.

Another highlight of the seminar will be a presentation of the results from HDA's Pilot Study for Saleable Returns, which was conducted earlier this year to further understand the operational impact of the DSCSA's 2019 requirements for distributors to verify serialized saleable returns from customers. A group of industry experts from various manufacturers and distributors conducted a study of nine real-life scenarios that would allow the pharmaceutical supply chain to comply with the requirements related to the 2019 implementation. HDA will outline the workable solutions that were identified through the pilot project.

Additional sessions will touch on meeting global traceability requirements, as well as perspectives from the retail/pharmacy community and technology experts on their priorities for implementation.

A full agenda, registration information and participating sponsors can be found on HDA's website.

Innovators and industry experts to introduce 'blockchain' applications to pharma supply chain executives

DisruptiveRx in partnership with **MAD Event Management** will be holding the Pharma Blockchain Bootcamp on Nov. 16 in Edison, NJ (http://www.RXBlockchainBootcamp.com) which an Oct. 13 news release said is the first blockchain seminar to exclusively address potential applications of this disruptive innovation throughout the bio/pharmaceutical enterprise.

The one-day seminar will present a business-technical introduction to blockchain technology, the most applicable areas that would benefit from its application, and the business, regulatory and legal considerations that must be considered when adopting this technology.

Blockchain is the platform used for Bitcoin monetary transactions. It is said to be foolproof to hacking. According to the definition, blockchain is constantly growing as 'completed' blocks are added to it with a new set of recordings. The blocks are added to the blockchain in a linear, chronological order. There has been some thought that blockchain could be used to secure drug transactions and supply chain integrity.

According to the release, the Pharma Blockchain Bootcamp will explore potential applications in three critical areas of the enterprise: R&D, clinical trials and supply chain. Four sessions will address how blockchain technology could better secure, manage and utilize data currently embedded within the supply chain framework. Sessions include: closing the gap between manufacturing and the supply chain; securing data transfer between trusted partners; safeguarding data networks from cyber-attacks and privacy breaches; and managing and leveraging data generated by the increase in serialization standards as a result of the 2013 DSCSA.

Driving the potential for blockchain applications within the enterprise is the growing demand for pharmaceutical companies to digitally transform their business model to optimize development and delivery of medicine. As a result of this digital transformation, they must ensure their IT infrastructure is flexible and collaborative to support the two-way flow of data at the quickest speed with the utmost security. And with that in mind, blockchain technology offers pharma the opportunity to revitalize its data strategy and effectively compete in the next generation of healthcare.

The Pharma Blockchain Bootcamp's educational program is designed for both business and technical leaders within the bio/pharmaceutical enterprise. The event is supported by the BlockRx Project, an industry initiative by **iSolve**, **the Center for Supply Chain Studies** and the **IEEE Standards Assn**. The Pharma Blockchain Bootcamp can only accommodate 50 pharmaceutical professionals; early discount registration is available through Oct. 31, 2016. For more information on registration and the educational program, please visit http://www.RxBlockchainBootcamp.com.

Shortages

FDA crack down on compounding leaves limited supplies of domperidone, new study finds

By Ken Reid, Editor

FDA's decision to place domperidone on the list of products not eligible to be compounded by pharmacies under the Drug Quality Standards Act (DQSA) has created a shortage of the drug, and only one supplier in the U.S., the conservative free-market **Goldwater Institute** said in a report issued Oct. 25.

The D.C.-based policy shop released an investigative report documenting FDA's efforts to cut off access to domperidone, a drug commonly used throughout the world to treat a potentially deadly medical condition called gastroparesis.

Domperidone is available in more than 100 countries, including Canada and throughout the European Union. In many of those countries it is sold over the counter. Since its introduction in 1978, domperidone has been a common treatment for such things as heartburn and bloating, as well as more serious conditions like gastroparesis.

In the past couple of years, FDA has been aggressively enforcing an import ban on domperidone. Patients who until recently had little trouble filling prescriptions for the drug can no longer get it. And people who had previously benefited from this drug are being forced off the only medication that has allowed them to live normal lives.

But in an email, the author of the study, Mark Flatten, said the placement of the drug on the Category 2 list (not to be compounded) has contributed to the shortage. Category 1 drugs can be compounded.

Flatten wrote in the email that prior to the adoption of DQSA in 2013, "pharmacies throughout the country were able to obtain bulk domperidone from international suppliers and use it to mix medications for individual patients because of the legal exceptions compounders enjoyed at the time. The 2013 law recognized that many drugs that were commonly being compounded at the time, though not approved by FDA through the IND/NDA process, were nonetheless needed by patients who had been able to get them from compounding pharmacies."

After passage of the 2013 law, Flatten wrote, "FDA did increase its enforcement of the import restrictions on domperidone, effectively drying up the supply. Since October 2015, when the compounding advisory committee placed domperidone on the Category 2 list, the only pharmacy that can still compound domperidone is **Dougherty's** in Texas for use in the expanded access program."

Several warning letters have been written to compounding pharmacies for making domperidone illegally.

The report said the only way to legally obtain the drug in the United States is through an FDA-authorized "expanded access" program. Agency officials refuse to say how many people are accessing the drug through its program.

FDA guidance for physicians who want to treat patients with domperidone shows they must agree to a litany of requirements which include developing monitoring and treatment plans for each patient, reporting adverse events and securing approval from institutional review boards, which aren't always readily available. Front-line physicians and medical professionals, and even members of FDA's own review committee, have called the agency's expanded access program unworkable, cumbersome and impractical.

Federal legislation is pending that would make drugs that have been approved in other developed countries like Canada, European countries, and Japan available to Americans without delay.

Read the new Goldwater Institute report Sickening: FDA Bureaucracy Blocks Common "Miracle Drug."

CMC

Promoting international cooperation and harmonization: EDQM-Chinese Pharmacopoeia Joint Workshop

Top representatives from the EDQM, the Chinese Pharmacopoeia Commission (ChP) and major trade associations gathered recently in Strasbourg for a one-day workshop, EDQM announced Oct. 26.

According to an agency news release, the event:

- introduced the content and scope of the 2015 edition of the Chinese Pharmacopoeia (ChP)
- provided the participants with a better understanding of the ChP's working methods
- encouraged an open exchange on pharmacopoeial issues with the audience

The EDQM also took the opportunity to present its newly released 9th Edition of the European Pharmacopoeia which comes into effect on Jan. 1, 2017, and to engage in bilateral discussions with the ChP about opportunities to strengthen collaboration in the future.

Dr. Susanne Keitel, Director of the EDQM, underlined that the EDQM is "continuously expanding its frontiers through new and close working relationships and partnerships worldwide in order to pool expertise and know-how." Therefore, she particularly welcomed this initiative, which gave all stakeholders an opportunity "to contribute to better public health for citizens in Europe and beyond."

Workshop materials are now available on these web sites:

- Workshop Program
- Workshop Slides
- More information on 9th Edition of the Ph. Eur. & How to order

Environmental

Antibiotic waste is polluting India and China's rivers, Guardian investigation says

Antibiotic-resistant superbugs are a fundamental threat to global health, United Nations secretary general Ban Ki-moon recently told a general assembly meeting. Failure to address the problem, he said, would make it "difficult if not impossible" to provide universal healthcare, "and it will put the sustainable development goals in jeopardy," "The Guardian" newspaper in England reported Oct. 21.

For pharmaceutical companies the attention on antimicrobial resistance has also brought a focus on one of its key drivers: the unabated environmental pollution of drug factories in developing countries.

In India and China, where a large proportion of antibiotics are produced, the poorly regulated discharge of untreated wastewater into soils and rivers is causing the spread of antibiotic ingredients which cause bacteria to develop immunity to antibiotics, creating superbugs.

A study of wastewater factories in China found that antibiotic-resistant bacteria were not only escaping purification but also breeding. For every bacterium that entered one waste treatment plant, four or five antibiotic-resistant bacteria were released into the water system, tainting water, livestock and communities.

Superbugs are able to travel quickly through air and water, aboard airplanes and through global food supply chains. By 2050, the total death toll worldwide as the result of contracting an infection that proves resistant to treatment is expected to reach 10 million.

Environmental pollution is now a material issue for the pharmaceuticals sector. Global investors such as **Nordea** and **BNP Paribas** have raised concern about the potential damage to global health and environment, and are worried that a local factory pollution scandal in India could affect the value of a global pharma company in their portfolio. As the world goes on a global quest to combat antimicrobial resistance, the focus on industry pollution will continue grow.

Last month 13 pharmaceutical companies signed a declaration calling for collective action on antimicrobial resistance. They committed to review their manufacturing and supply chains and assess good practice in controlling releases of antibiotics into the environment. They also committed to establish science and risk-based targets for discharge concentrations of antibiotics and to reduce the environmental impact of manufacturing discharges by 2020.

Most global sectors now have a corporate platform where companies seek to tackle intractable sustainability challenges. For pharma companies, the Pharmaceutical Supply Chain Initiative (PSCI) was set up to demand better social and environmental conditions in the communities from where drugs are supplied. However, only 12% of the 140 largest global pharmaceutical companies are members of PSCI, according to sector analysts.

Voluntary corporate initiatives are necessary but by no means sufficient to address the industry challenge of environmental pollution. This is partly because not every company signs up and partly because better government policies and law enforcement on the ground are necessary to ensure voluntary commitments are achievable.

The governments where global pharma companies are domiciled – including the UK, U.S. and Switzerland – must play a role. Companies must

collaborate with governments to encourage and support a tougher stance on law enforcement in developing counties.

The aid budget of agencies such as the UK Department for International Development could be used to strengthen pollution controls in sourcing countries such as India. This would be a win-win for health in developing countries and for national business interests abroad.

Through the PSCI, the global pharmaceutical industry has called upon governments to collaborate on the threat of increasing antibiotic resistance. PSCI must now also urgently work with governments to achieve the goal of curbing environmental pollution in drug manufacturing.

Ultimately, business diplomacy goes beyond corporate philanthropy and corporate social responsibility, by focusing on the deeper governance failures that threaten progress on sustainable development as well as the license to operate of global companies. Pharmaceutical companies now need to cooperate with governments, to root out pollution from their global supply chains.

Drug review

FDA withdraws generics for Concerta extended release tablets by Mallinckrodt, Kudco

FDA is proposing to withdraw approval of two generic versions of Concerta (methylphenidate hydrochloride) extended-release (ER) capsules, used to treat attention-deficit hyperactivity disorder.

Mallinckrodt Pharmaceuticals and **UCB/Kremers Urban** (formerly **Kudco**), the companies that make the generic products, "have failed to demonstrate that their products provide the same therapeutic effect as (are bioequivalent to) the brand-name drug they reference," FDA said in its Oct. 17 announcement.

This action is related to steps FDA took in November 2014. At that time, FDA announced that, based on an analysis of data, it had concerns that the Mallinckrodt and Kudco products may not produce the same therapeutic effects as Concerta. FDA requested that Mallinckrodt and Kudco either voluntarily withdraw their products from the market and request that FDA withdraw approval of their product's Abbreviated New Drug Applications (ANDAs) or, within six months, provide data to confirm that their products are bioequivalent to Concerta consistent with the revised draft guidance for industry for bioequivalence testing for these products.

At that time, FDA changed the Orange Book therapeutic equivalence code for these two products from AB (indicating therapeutic equivalence) to BX (data are insufficient to determine therapeutic equivalence).

Neither Mallinckrodt nor UCB/Kremers Urban has voluntarily withdrawn its product from the market, and neither has provided data confirming its product's bioequivalence consistent with the revised recommendations. Accordingly, FDA is proposing to withdraw approval of the products' ANDAs and is announcing an opportunity for the firms to request a hearing on the proposal. As part of this process, FDA is publishing Notices of Opportunity for Hearing (NOOHs) on its Proposals to Withdraw Marketing Approval in the Federal Register. If approval of these ANDAs is withdrawn by FDA, the products will no longer be able to be marketed in the U.S.

Each NOOH explains that the firm may request a hearing to show why approval of their ANDA should not be withdrawn and has the opportunity to raise, for administrative determination, all issues relating to the legal status of the drug products covered by these applications. Each firm must respond in writing, within 30 days, to request a hearing. If the firm fails to do so, the opportunity for a hearing will be waived.

During the course of this process, FDA will update the related Mallinckrodt and UCB/Kremers Urban dockets as new information becomes available.

The Mallinckrodt UCB/Kremers Urban products are still approved and can be prescribed, but they are not recommended as automatically substitutable for Concerta. **Janssen** manufactures an authorized generic of Concerta, which is marketed by **Actavis** under a licensing agreement. The Actavis product is not impacted by this announcement.

If you or your health care professional are concerned that a methylphenidate hydrochloride ER product you are taking is not providing the desired effect, and you do not know the manufacturer, contact the pharmacy where the prescription was filled to verify the product's manufacturer. If you, or those under your care, are taking the Mallinckrodt or Kudco products and have concerns about lack of desired effect during the dosing period, contact the prescribing health care

provider to discuss whether a different drug product would be more appropriate.

FDA has not identified any serious safety concerns with these two generic products. Patients should not make changes to their treatment except in consultation with their health care professional.

Drug & device safety

EMA recommends measures to ensure safe use of Keppra oral solution; medicine should only be used with dosing syringe included in the package

Several measures have been put in place to ensure that the correct dosing syringe is used to measure Keppra oral solution, and thus avoid medication errors, the European Medicines Agency announced Oct. 14.

Keppra (levetiracetam) is a medicine for the treatment of epilepsy. It can be used on its own in patients from 16 years of age with newly diagnosed epilepsy, to treat partial-onset seizures with or without secondary generalization. It can also be used as an add-on to other antiepileptic medicines to treat partial-onset seizures with or without generalization in patients from one month of age; myoclonic seizures in patients from 12 years of age with juvenile myoclonic epilepsy; and primary generalized tonic-clonic seizures in patients from 12 years of age with idiopathic generalized epilepsy.

Keppra is available as an oral solution, as tablets and as a solution for infusion (drip) into a vein.

Several generics of Keppra are marketed in the European Union. Companies that market generic levetiracetam oral solutions are also expected to use colors to differentiate one presentation from another, and to clearly indicate on the package and the label the age range of the child that the presentation should be used for, and which dosing device should be used.

In children, the dose of Keppra depends on the child's body weight and age, and the oral solution is the preferred formulation for use in children under six years of age. The medicine is available as a 100 mg/ml solution in either a 150 or 300 ml size bottle, and it comes with a 1-, 3- or 10-ml syringe.

Cases of accidental overdose have been reported with levetiracetam oral solution; the majority of cases occurred in children aged between 6 months and 11 years. Most of the cases occurred when the medicine was used with a wrong dosing syringe (e.g., a 10-ml syringe was used instead of a 1 ml one, leading to a 10-fold overdose), or because of a misunderstanding of the caregiver about how to properly measure the dose. Levetiracetam overdose often has no symptoms, but it may cause sleepiness, agitation, difficulty breathing and coma.

To avoid medication errors and the risk of overdose, parents and caretakers are advised that only the syringe provided with the package should be used to measure the dose of Keppra. The different medicine's cartons and labels will be colored differently and clearly indicate the volume of the bottle, the volume of the dosing syringe, and the age range of the child that the medicine should be used for:

The package leaflet will also include clearer instructions for parents and caretakers in order to minimize the risk of using an incorrect dose. Parents and caretakers are advised always to discard the syringe once the medicine's bottle is empty.

The outer packaging and bottle labels of Keppra 100 mg/ml oral solution will use colors to better differentiate each presentation: blue for the 150-ml bottle with 1-ml syringe; green for the 150-ml bottle with 3-ml syringe; and orange for the 300-ml bottle with 10-ml syringe.

Health care professionals should follow these recommendations:

- Doctors should ensure that the age-appropriate presentation of Keppra is prescribed.
- Doctors should always prescribe the dose in milligrams with milliliter equivalence based on the correct age of the patient.
- Pharmacists should ensure that the appropriate presentation of Keppra is dispensed.
- With every prescription, health care professionals should advise the patient and/or caregiver on how to measure the prescribed dose.
- With every prescription, health care professionals should remind patients or caregivers to use only the syringe included in the medicine's package. Once the bottle is empty, the syringe should be discarded.

The cases of overdose with levetiracetam oral solution were reviewed in the context of a safety

signal evaluation. A safety signal is information on a new or incompletely documented adverse event that is potentially caused by a medicine and that warrants further investigation.

The review of this safety signal was carried out by the Pharmacovigilance Risk Assessment Committee (PRAC), the Committee responsible for the evaluation of safety issues for human medicines. The PRAC recommendations were sent to the Committee for Medicinal Products for Human Use (CHMP), responsible for questions concerning medicines for human use, which endorsed them. The company that markets Keppra is expected to take action according to the recommendations.

FDA announces mycobacterium chimaera infections associated with LivaNova PLC Stockert 3T Heater-Cooler System

FDA Oct. 13 updated its June 1, 2016, Safety Communication to provide new information about *Mycobacterium chimaera* (*M. chimaera*) infections associated with the use of the Stockert 3T Heater-Cooler System (3T) in U.S. patients who have undergone cardiothoracic surgeries. This communication also contains updated recommendations to help prevent the spread of infection related to the use of these devices.

The device, manufactured by **LivaNova PLC** (formerly **Sorin Group Deutschland GmbH**, is intended to provide temperature-controlled water to oxygenator heat exchangers, cardioplegia (paralysis of the heart) heat exchangers, and/or warming/cooling blankets to warm or cool a patient during cardiopulmonary bypass procedures lasting six hours or less.

Heater-cooler devices are commonly used during cardiothoracic surgeries, as well as other medical and surgical procedures, to warm or cool a patient in order to optimize medical care and improve patient outcomes. Heater-cooler devices have water tanks that provide temperature-controlled water to external heat exchangers or warming/cooling blankets through closed circuits.

Although the water in the circuits does not come into direct contact with the patient, there is the potential for contaminated water to enter other parts of the device and aerosolize, transmitting bacteria through the air and through the device's exhaust vent into the environment and to the patient.

In October 2015, FDA issued a Safety Communication to provide recommendations to help minimize patient risk of infections associated with heater-cooler devices. Since issuing that communication, FDA has continued to evaluate the causes and risk factors for transmission of microbial agents associated with heater-cooler devices and has collaborated with professional societies, public health partners and experts to develop strategies to minimize patient exposure.

A European study published in April 2016 describes a link between *M. chimaera* clinical samples from several European infected cardiothoracic patients, samples from the heater-cooler devices used during these patient's procedures, and environmental samples from the device manufacturer's production and servicing facility in Germany. The results of this paper suggest a direct link between the *M. chimaera* that infected European patients during open-chest cardiac surgery and the *M. chimaera* isolated from the 3T heater-cooler model utilized during these patients' surgeries.

M. chimaera is a type of nontuberculous mycobacterium (NTM) classified as a slow grower. *M. chimaera* may cause serious illness or death. FDA believes *M. chimaera* infections associated with the 3T are rare. However, they are difficult to detect because infected patients may not develop symptoms or signs of infection for months to years after initial exposure.

On June 1, FDA issued a Safety Communication specific to *M. chimaera* infections associated with the use of the 3T. Testing conducted by the manufacturer in August 2014 found *M. chimaera* contamination on the production line and water supply at the 3T manufacturing facility. The 3T devices manufactured at this facility were distributed worldwide. In response to the *M. chimaera* findings in August 2014, the manufacturer added cleaning and disinfection procedures to the production line in September 2014.

Samples taken at the same manufacturing facility by the German Regulatory Authorities in July 2015 did not show *M. chimaera*, potentially indicating the contamination at the manufacturing facility had been resolved. Although the manufacturer of 3T devices added cleaning and disinfection procedures to the production line in September 2014, FDA is now aware of some 3T devices manufactured after September 2014 which have tested positive for *M. chimaera*. It has not been confirmed whether these devices were contaminated at the manufacturing facility or became contaminated at the user facility. To date, FDA is not aware of *M. chimaera* patient infections associated with

3T devices that were manufactured after September 2014.

The June 1 Safety Communication also stated FDA received reports of U.S. patients infected with *M. chimaera* after undergoing cardiothoracic surgery that involved use of the 3T devices. Each of those reports related to 3T devices that were manufactured prior to September 2014.

The Centers for Disease Control and Prevention (CDC) in conjunction with **National Jewish Health** has performed whole genome sequencing on clinical isolates from infected patients and samples taken from the 3T devices from hospitals representing geographically distinct regions within the U.S. (Pennsylvania and Iowa) where clusters of patient infections with *M. chimaera* were identified. Each of the isolates tested were associated with devices manufactured before September 2014.

Samples of the water drained from the 3T devices and air samples collected while the devices were in operation were also tested. The results obtained strongly suggest that the tested 3T devices had a common source of *M. chimaera* contamination. Sequence comparisons between U.S. and European Union (EU) samples, as well as samples from the manufacturing site, would provide additional information in evaluating the potential for point source contamination at the production site. However, EU sequencing results have not been shared to date.

FDA recommended the health care providers using the device do the following:

- Immediately remove from service any heater-cooler devices, accessories, tubing, and connectors that have tested positive for *M. chimaera* or have been associated with known *M. chimaera* patient infections at your facility.
- Use new accessories, tubing, and connectors to prevent recontamination when using a different heater-cooler device.
- Direct and channel the heater-cooler exhaust away from the patient, e.g., to the operating room exhaust vent.
- Be aware that device contamination also may occur from other sources such as environmental contamination or device contact with contaminated accessories.
- Review the recommendations in CDC's Health Advisory
- Be aware that heater-cooler devices are important in patient care. In appropriately selected patients, the benefits of temperature control during open chest cardiothoracic procedures generally outweigh the risk of infection transmission associated with the use of these devices.

Additional information for patients is available on FDA's Heater-Cooler Devices "Information for Patients" webpage.

FDA also noted that on Dec. 29, 2015, the agency issued a Warning Letter to LivaNova PLC (formerly **Sorin Group Deutschland GmbH**) for its Stockert 3T Heater-Cooler System after inspections conducted at facilities in Munchen, Germany and Arvada, CO, revealed significant issues, including quality system and premarket clearance violations. Given the serious nature of the violations, the 3T devices manufactured by the Munchen facility are subject to import alert. This restricts the availability of the 3T devices to only those facilities that determine use of the device is medically necessary.

Sorin Group Deutschland GmbH initiated an ongoing corrective action for the 3T in July 2015, and has included updates to instructions for use with new cleaning instructions and instructions for determining if a device is contaminated with biofilm or NTM. Further updates to this recall are expected and will be evaluated by FDA for their ability to further reduce infection risk. Please see FDA medical device recall database entry for more information regarding corrective actions by the manufacturer.

In June 2016, FDA convened the Circulatory System Devices Panel of the Medical Devices Advisory Committee meeting and received expert clinical opinion and recommendations for patient notification and patient follow-up procedures. The panel also discussed recommendations for sampling and monitoring of the 3T and other heater-cooler devices, including regular visual monitoring of contamination within the water circuit, replacement of accessories (e.g. tubing) on a regular basis, and testing for water quality to assure adequate disinfection procedures are being performed. These recommendations are included in this Safety Communication.

The agency listed the following resources on the device:

- **FDA Communications on Heater-Cooler Devices**
  - Mycobacterium chimaera Infections Associated with Sorin Group Deutschland GmbH Stöckert 3T Heater-Cooler System: FDA Safety Communication (June 1, 2016) - ARCHIVED
  - Nontuberculous Mycobacterium Infections Associated with Heater-Cooler Devices: FDA Safety Communication (Oct. 15, 2015)
  - Heater-Cooler Informational Webpage
- **From the Centers for Disease Control and Prevention (CDC)**

- Perkins KM, Lawsin A, Hasan N, et al. *Mycobacterium chimaera Contamination of Heater-Cooler Devices Used in Cardiac Surgery — United States*. MMWR Morb Mortal Wkly Rep 2016;65:1117–1118. DOIhttps://emergency.cdc.gov/han/han00397.asp
- CDC Health Advisory: CDC Advises Hospitals to Alert Patients at Risk from Contaminated Heater-Cooler Devices Used during Cardiac Surgery (Oct. 13, 2016)
- Interim Guide for the Identification of Possible Cases of Nontuberculous Mycobacterium Infections Associated with Exposure to Heater-Cooler Units (May 13, 2016)
- Non-tuberculous Mycobacterium (NTM) Infections and Heater-Cooler Devices (Oct. 27, 2015)

- **Medical Literature:**
  - Sommerstein et al. **Transmission of *Mycobacterium chimaera* from Heater-Cooler Units during Cardiac Surgery despite an Ultraclean Air Ventilation System.** Emerg Infect Dis. 2016 June;22(6):1008-13.
  - Garvey et al.**Decontamination of heater-cooler units associated with contamination by atypical mycobacteria**. J. Hospital Infection, Volume 93, Issue 3, July 2016:229-34.

FDA warns batteries in some St. Jude defibrillators may fail earlier than expected

FDA and **St. Jude Medical** are alerting patients, patient-caregivers and physicians to respond immediately to Elective Replacement Indicator (ERI) alerts, and issue that has led FDA and the company to be involved in the cybersecurity issue involving the devices (see story below).

The company said it would recall some of its 400,000 implanted heart devices due to risk of premature battery depletion, a condition linked to two deaths in Europe, according to Reuters.

Due to problems with these batteries, patients do not have the normal three-month lead time for device replacement. Some batteries have run out within 24 hours of the patient receiving an ERI alert. St. Jude Medical has initiated a recall and correction of the affected devices. See the FDA Safety Communication for a listing of affected devices and data summary.

St. Jude Medical has reported that in some cases, full battery drainage can occur within a day to a few weeks after the patient receives an ERI alert. If the battery runs out, the ICD or CRT-D will be unable to deliver life-saving pacing or shocks, which could lead to patient death. The patients most at risk are those with a high likelihood of requiring life-saving shocks and those who are pacemaker dependent.

Battery depletion may not always be reported to the manufacturer; therefore, the true number of devices with premature battery depletion due to lithium clusters is not known. At this time, 349,852 affected devices remain actively implanted worldwide.

FDA will continue to monitor affected St. Jude Medical ICD and CRT-D devices for any adverse events related to premature battery depletion or cybersecurity vulnerabilities, and the agency will keep the public informed as new information becomes available.

Implanted defibrillators (ICDs and CRT-Ds) are powered by lithium-based batteries. Deposits of lithium, known as "lithium clusters," can form within the battery and create a billion normal electrical connections leading to rapid battery failure.

See the FDA Safety Communication for a complete listing of recommendations for health care providers and patients. For health care professionals:

- Do not implant unused affected devices. Premature battery depletion due to lithium clusters has only been observed in devices manufactured prior to May 2015. At this time, there is no information indicating that this issue affects devices manufactured after this date.
- Communicate with all patients who have an affected device that their device has a battery that may run out earlier than expected. Consider giving patients the Dear Patient letter provided by St. Jude Medical.
- Continue to conduct follow-up on patients with affected devices using in-office visits in addition to remote monitoring once they have been notified of the battery issue. Increased in-office surveillance is not necessary for patients who are also followed with remote monitoring.
- Immediately replace the device at the time of an ERI alert. Currently, there is not a factor, method or test to identify when devices with this form of premature battery depletion are approaching ERI, or to accurately predict remaining battery life once ERI appears.
- Pacemaker-dependent patients with a device that has reached ERI should be treated as a medical emergency.

- Health care providers should consider whether elective device replacement is warranted for their pacemaker dependent patients. Ultimately, health care providers should individualize the care of their patients based on the patients' medical history, comorbidities and condition.
- Most patients will not require prophylactic device replacement prior to ERI, as the rate of complications following replacement surgery are higher than those associated with premature battery depletion. However, FDA and St. Jude Medical recognize the need to weigh individual clinical considerations. If the decision is made to replace an affected device based on individual patient circumstances, St. Jude Medical has announced they will provide a replacement device at no cost.
- Enroll patients in Merlin@Home, St. Jude Medical's home monitoring system for these devices, especially those who have difficulty recognizing their device's ERI alerts. For patients already enrolled in Merlin@Home, explain the importance of ongoing home monitoring. Utilize the "Direct Alerts" feature to provide you with an alert notification when a patient's device has reached ERI. Please see additional information about the Merlin@Home Monitoring System below. If a home monitor is ordered for a patient with an affected device, St. Jude Medical will cover the cost of the home monitor.
- Ensure that the ERI battery alert is ON for all patients. Review the most recent "Programmed Parameters" printout.

Read the MedWatch safety alert at: http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm524706.htm

St. Jude to establish cybersecurity advisory board due to issues with devices; FDA investigates with U.S. Department of Homeland Security

St. Jude Medical said Oct. 17 it planned to set up a medical advisory board focused on cyber-security issues affecting patient care and safety due to issues with its cardiovascular devices, **Reuters** reported.

In a subsequent FDA announcement about the recall of the ICDs, FDA said it "recommends that patients, patient caregivers and health care providers enroll in and utilize the St. Jude Medical Merlin@Home monitoring system to help detect battery depletion. FDA is investigating cybersecurity concerns associated with these devices, including the Merlin@Home."

The agency added:

"FDA (in partnership with the Department of Homeland Security ICS-CERT) continues to investigate recent allegations of cybersecurity vulnerabilities associated with St. Jude Medical cardiac devices, including the Merlin@Home monitoring system. Despite the allegations, at this time, FDA strongly recommends that the Merlin@Home device be used to monitor the battery for these affected devices. The ICD and CRT-D devices identified in this safety communication provide life-saving therapy, and FDA believes that the benefits of monitoring outweigh any potential cybersecurity vulnerabilities."

St. Jude is creating a cybersecurity advisory group to advise on issues involving medical devices. The group has not been finalized as of yet, but will consist of medical and cyber experts...

FDA launched that probe in August after short-seller **Muddy Waters** and cyber research firm **MedSec Holdings** said they had placed bets that St. Jude shares would fall after they discovered the alleged vulnerabilities.

St. Jude said in a statement that the group, known as the **Cyber Security Medical Advisory Board**, would provide advice on cyber security standards for medical devices.

"We take the cyber security of our devices very seriously and creating the Cyber Security Medical Advisory Board is one more demonstration of our ongoing commitment to advancing standards of patient care around the world without comprising safety and security," St. Jude Chief Medical Officer Mark Carlson said in a statement.

The board, whose membership has yet to be finalized, will work with technology experts at St. Jude Medical as well as external researchers to help "maintain and enhance cyber security and patient safety," Carlson said.

Suzanne Schwartz, a senior official in FDA's Center for Devices, said the agency supports efforts by medical device manufacturers to prioritize cyber security.

"Doing so in collaboration with other stakeholders such as cyber security researchers, health care providers, patients and government agencies, means cyber security vulnerabilities are more likely to be identified, assessed and fixed in a timely manner before they can cause patient harm," she said in a statement.

FDA unveils new labeling for testosterone drugs

FDA Oct. 24 announced it has approved class-wide labeling changes for all prescription testosterone products, adding a new Warning and updating the Abuse and Dependence section to include new safety information from published literature and case reports regarding the risks associated with abuse and dependence of testosterone and other anabolic-androgenic steroids (AAS.)

The Anabolic Steroids Control Act of 1990 placed AAS, including testosterone, in Schedule III of the Controlled Substances Act. Testosterone and other AAS are abused by adults and adolescents, including athletes and body builders. Abuse of testosterone, usually at doses higher than those typically prescribed and usually in conjunction with other AAS, is associated with serious safety risks affecting the heart, brain, liver, mental health and endocrine system.

Reported serious adverse outcomes include heart attack, heart failure, stroke, depression, hostility, aggression, liver toxicity and male infertility. Individuals abusing high doses of testosterone have also reported withdrawal symptoms, such as depression, fatigue, irritability, loss of appetite, decreased libido and insomnia.

The new Warning will alert prescribers to the abuse potential of testosterone and the serious adverse outcomes, especially those related to heart and mental health that have been reported in association with testosterone/AAS abuse. In addition to the new Warning, all testosterone labeling has been revised to include information in the Abuse and Dependence section about adverse outcomes reported in association with abuse and dependence of testosterone/AAS, and information in the Warning and Precautions section advising prescribers of the importance of measuring serum testosterone concentration if abuse is suspected.

Prescription testosterone products are FDA-approved as hormone replacement therapy for men who have low testosterone due to certain medical conditions. Examples of these conditions include failure of the testicles to produce testosterone because of genetic problems, or damage to the testicles from chemotherapy or infection.

For more information, please visit: Testosterone

FDA splits on naloxone dose

A joint meeting of FDA's Anesthetic and Analgesic Drug Products Advisory Committee and Drug Safety and Risk Management Advisory Committee failed to produce consensus on the minimum dose of naloxone needed to reverse the effects of opioid overdose, the **American Pharmacists Assn.** reported in its Oct. 12 newsletter.

A total of 13 members agreed that the current injectable standard of 0.4 mg is effective and should remain in place—many of them expressing concern that raising it could send patients into withdrawal—but 15 argued for a higher minimum dose based on the trend toward abuse of ever more powerful opioids. Voters on both sides agreed, however, that evidence to make an informed decision was lacking.

While the issue of minimum dose remains unresolved, the panelists were somewhat more definitive in a vote on whether to have the same minimum dose for children and adults. In that case, the count was 21-7 to keep those numbers consistent.

Compliance/enforcement

Akorn plant cited in FDA Form 483

Akorn has received a 483 regarding GMP issues at its plant in Decatur, IL, **FiercePharmaManufacturing.com** reported Oct. 19.

The highly redacted report, posted on the FDA website, shows that a June inspection at a plant on Grand Avenue led to half a dozen observations.

Among the problems cited were media fill line issues that plant managers acknowledged should have led to halting production of a commercial batch but which they said was allowed to proceed. On top of that, some media fills were not overseen by quality control personnel and much of the work was not logged.

Inspectors also pointed out that both foreign matter and cracked vials were found in a sublot of the antibiotic clindamycin, but the plant never got to the root cause of the issues and failed to see if other sublots were similarly affected.

The inspectors also questioned the plant's rationale for its sampling procedures as well as raising concerns about environmental monitoring.

This comes on top of the recalls that Akorn and its **Hi-Tech Pharmacal** unit have been wrestling with. In March, **Actavis** began voluntarily recalling 24 lots, amounting to 447,150 bottles, of ciprofloxacin ophthalmic solution that were manufactured by Hi-Tech. The solution failed impurities and degradation specs for an unknown impurity. Before that, Hi-Tech recalled 57,920 bottles of sulfacetamide sodium ophthalmic solution that failed antimicrobial effectiveness testing.

Teva's struggling sterile plant hit with FDA warning letter

The regulatory quagmire has deepened for the **Teva Pharmaceutical** sterile injectables plant in Hungary which FDA banned this year over slipshod manufacturing standards. FDA has now issued the plant a warning letter, **FiercePharmaManufacturing.com** reported Oct. 19.

In an SEC filing, Israel-based Teva acknowledged receiving the warning letter the previous Friday, and for the first time gave some indication of the problem areas. It said FDA "cited deficiencies in manufacturing operations and laboratory controls, and in the Company's data integrity program."

In an emailed statement, Teva said it "has been using a systems-based approach with respect to our remediation efforts," addressing both the FDA concerns and the underlying causes. "As a matter of practice, Teva manufactures according to the highest quality and compliance standards."

The company also said it is working to resupply "critical and priority products as quickly as possible," by bringing in products from other Teva manufacturing sites and finding other suppliers for products in short supply or out of stock.

The warning letter follows a series of other actions by FDA, which first issued a 483 following a two-week inspection in January at the Godollo plant, a relatively new facility the company opened in 2012 to expand its injected drug capacity. Teva suspended production to deal with the citations but FDA in May put the plant on its import alert list, banning all but two drugs—the cancer treatment bleomycin and antibiotic amikacin— which were exempted to avoid shortages. Teva has been recalling from the market its other drugs produced at the facility.

The regulatory issues come when Teva has a lot on its plate. It is in the process of assimilating a huge portfolio of products, plants and employees it got in its $40.5 billion buyout of **Allergan's** generics business, while selling off those parts of the business required by regulators to preserve competitive markets.

But Teva has suggested it may not be done with acquisitions to solidify its place as the largest maker of generic drugs, while also looking at moves in the branded market. A Teva spokesperson said the company would consider opportunities in biosimilars, suggesting to some that Teva might look at buying South Korea's **Celltrion**. Celltrion is trying to sell part of its business and the two have a relationship.

CEO Erez Vigodman has said the biosimilars are part of the company's growth strategy but also said it will be on the hunt for "attractive specialty assets, or branded drug assets or pipeline assets" that fit in with the therapeutic areas it's already tackling.

EMA castigates Nandu Chemicals site for failing everything GMP

French regulators have identified another Indian API maker they say lacks just about every kind of good manufacturing practice needed to produce acceptable drugs, sanitation, data integrity and sample control. As a result, they have recommended the European Medicines Agency recall all of its products and not allow them to be used in any new drugs, **FiercePharmaManufacturing.com** reported Oct. 17

The recommendations come after an August inspection of the **Nandu Chemicals Industries** in Hubli. Inspectors were there primarily to look over Nandu's manufacturing of zinc sulphate but said the company makes many other APIs.

The report, published on the EudraGMP site said, "Significant deficiencies were observed in the vast majority of inspected areas." In particular, it found "falsification practices...and inadequate control systems" across the site.

On top of that, inspectors reported the facility lacked basic hygiene practices in the packing area and inadequate standards for retaining samples for stability studies. Cleaning was subpar and the facility was not carefully monitoring the quality of the purified water.

The French agency suggested that the EMA order the recall of all of Nandu's products from the European market and require drugmakers to drop it as an API supplier.

Nandu joins a long list of Indian and Chinese API makers against which the EMA has taken actions. Following an inspection earlier this year by Italian regulators, the EMA recommended recalls of all of the products produced at a **JP Laboratories** unit in Maharashtra and a **Krebs Biochemicals & Industries** plant in Andhra Pradesh.

Recalls/warnings

Allergan recalls some Tazorac acne gel

Allergan, which made its name with dermatology products like Botox, recalled more than 42,000 tubes of an acne gel that failed to meet specifications during stability testing, **FiercePharmaManufacturing.com** reported Oct. 20.

According to the most recent FDA Enforcement Report, Allergan recalled 42,359 tubes of Tazorac in 30-g and 100-g sizes because the gel at the 24-month stability test fell slightly below regulatory specifications for product concentration and content uniformity.

In a letter to retailers, Allergan said the health risk is slight because the product is below specs and that it has not received any reports of adverse events. The voluntary recall actually began in June but was only classified last week by the FDA and posted on its web site.

Allergan last year recalled about 50 lots of some of the eye ointments sold under the brands Refresh, Lacri-Lube and others after receiving a dozen consumer complaints of a small black particle in the product. Allergan determined that the particle was created when unscrewing the cap from the aluminum tube and in some cases getting into the ointment.

Allergan had some other recalls this year, but those were tied to the **Actavis** generics unit it was recently sold to Teva for $40.5 billion.

Pii produced products recalled by Teva

Teva is recalling nearly 43,000 bottles of paricalcitol, a drug used by dialysis patients, which was produced by **Pharmaceutics International Inc.** (Pii) a U.S. contract manufacturing organization (CMO) that recently ran into problems with European regulators, **FiercePharmaManufacturing.com** reported Oct. 20.

According to the most recent FDA Enforcement Report, Teva is recalling 42,969 bottles of paricalcitol in three dose sizes in 30-count bottles, 32,015 of 1 mcg bottles; 5,556 of 2 mcg bottles and 5,398 of 4 mcg bottles. Paricalcitol is used to treat and prevent overactive parathyroid glands in patients with chronic kidney disease who are on dialysis.

The voluntary recall, which began several weeks ago, was initiated because the products failed stability testing for impurity levels.

The paricalcitol, the FDA report says, was manufactured by Hunt Valley, MD-based Pii. Several months ago, the European Medicines Agency said it was pulling the manufacturing certification for the contract manufacturer after inspectors noted a number of problems. In the critical category was Pii's failure to minimize the risk of cross-contamination between hazardous and nonhazardous products, the report said. Inspectors also noted the facility had an unqualified HPLC system and unacceptable approach to production equipment qualification.

In response, the company "brought in a team of experts" to address each area of concern and says it is giving the EMA's action top priority.

While this recall falls on Pii, Teva is facing manufacturing concerns of its own. FDA last week issued a warning letter to Teva' sterile manufacturing plant in Hungary, a facility that earlier this year was banned from exporting most products to the U.S.

Teva says it is conscientiously addressing the FDA's concerns and their underlying causes.

HeartWare initiates Class I recall of Ventricular Assist Device (HVAD) Pumps due to contamination-causing electrical issues

HeartWare Inc. is recalling the HVAD pumps due to a design problem with the driveline connector, FDA reported Oct. 25.

According to the Class I recall report, the driveline is a tube that connects the HVAD's pump to the external controller and power source. Contamination of the driveline may result in fluid or other material entering the pump and causing electrical issues or pump stops that may lead to serious adverse health consequences, including death.

The HVAD helps deliver blood from the heart to the rest of the body. It is used in patients who are at risk of death from end-stage left ventricular heart failure and who are waiting for a heart transplant. The system includes a pump implanted in the space around the heart (pericardium) and a controller that controls the speed and function of the pump.

The HVAD is designed for use both in and out of hospital settings, including during patient transport. This recall affects all HVADs with serial numbers lower than HW25838, Product Codes 1103 and 1104, manufacturing dates: March 17, 2006 to June 27, 2016. 105 units have been recalled in the U.S.

On Aug. 17, 2016, HeartWare Inc. sent an "Urgent Medical Device Recall Letter" to affected customers. The letter instructed consumers to:

- Identify affected HVADs in hospital inventory
- Complete and return the "Acknowledgement Form" attached to the letter
- Return affected products to HeartWare Inc.
- After returning the affected products, complete and return the "Completion Form" to a HeartWare representative no later than 2 months from the date on the letter
- Remind their patients about the safe use of the HVAD System, particularly with regard to moisture and proper connection to power and data sources.

Health care providers who have questions should contact their HeartWare representative or contact HeartWare Inc. at cs@heartware.com or 1-877-367-4823 with any questions related to this recall.

Medtronic announces voluntary recall of Pipeline embolization device, Alligator retrieval device, X-celerator hydrophilic guidewire, ultraflow and marathon flow directed micro catheters

Medtronic Oct. 11 announced that it has notified customers of a voluntary recall of certain lots of its Pipeline embolization device, Alligator retrieval device and X-Celerator hydrophilic guidewire. The recall also includes the stylet containing UltraFlow flow-directed microcatheters and Marathon flow-directed microcatheters. These products are produced, marketed and sold by Medtronic's Neurovascular business, which is part of the Brain Therapies division in the company's Restorative Therapies Group.

This voluntary recall is being conducted due to the potential separation and detachment of the polytetrafluoroethylene (PTFE) coating on parts of these devices. Should the PTFE separate from the delivery wire or stylets, PTFE particulate could enter the blood stream of the patient. PTFE in the blood stream, based on the size and quantity, could lead to a thromboembolic event.

Medtronic initiated customer communication of the recall by letter on Oct. 5, 2016, and is requesting customers to quarantine all affected product that remain in the inventory and return to Medtronic. FDA and other regulatory bodies also have been notified, the firm said in its news release.

At the initiation of this recall, 84,278 units potentially affected by this recall had been distributed

worldwide. The products were manufactured from July 2014 to Sept. 2016. Additional information about the recall, including the specific lot numbers of affected product, can be found at http://bit.ly/2dTvety.

Medtronic is taking this voluntary action as a precaution and has received no reports of patient injuries to date related to this issue. The full recalled product list of affected lot totals is itemized below:

The Pipeline embolization device is indicated for the endovascular treatment of adults (22 years of age and older) with large or giant wide-necked intracranial aneurysms in the internal carotid artery from the petrous to the superior hypophyseal segments. The first generation Pipeline embolization device is affected by this action due to the PTFE coated delivery wire, which is part of the disposable delivery system (the braid implant is not affected). The second-generation device, Pipeline Flex embolization device, is not affected by this recall.

The voluntary recall is being conducted due to the potential separation and detachment of the polytetrafluoroethylene (PTFE) coating on parts of these devices. Should the PTFE separate from the delivery wire or stylets, PTFE particulate and enter the blood stream of the patient, it could lead to a thromboembolic event...

The Alligator retrieval device is intended for use in the peripheral and neurovasculature for foreign body retrieval. The X-Celerator hydrophilic guidewire is indicated for general intravascular use to aid in the selective placement of catheters in the peripheral, visceral and cerebral vasculature during diagnostic and/or therapeutic procedures.

The UltraFlow flow-directed microcatheter is designed for the subselective infusion of physician-specified therapeutic agents such as embolization materials and diagnostic materials such as contrast media in tortuous, distal vessels. The Marathon flow-directed microcatheter is intended to access peripheral and neurovasculature for the controlled selective infusion of physician-specified therapeutic agents such as embolization materials and of diagnostic materials such as contrast.

Click here to read the full MedWatch/Medtronic announcement: http://www.fda.gov/Safety/Recalls/ucm525582.htm?source=govdelivery&utm_medium=email&utm_source=govdelivery

Leonhard Lang initiates Class I recall of Skintact DF29N Multi-function Defibrillation Electrodes due to connector compatibility issue

The **Leonhard Lang** defibrillation electrode is being recalled due to a connector compatibility issue with the **Welch Allyn** AED model 10. The user may not be able to connect the electrodes to the defibrillator when a shock is needed. This may result in a delay in delivering the electrical therapy needed to revive a patient in cardiac arrest.

A delay in therapy could result in serious patient injury and/or death.

Recalled product details:

- 50028 Defibrillation Electrode SKINTACT DF29N
- Lot Numbers: 60602-0774, 60502-0779, 60308-0771,60114-0773, 51023-0775, 50904-0777, 50403-0778, 50130-0777, 41023-0771, 41008-0778 40730-0778, 40618-0778, 40130-0776
- Distribution Dates: Feb. 14, 2014, to Aug. 3, 2016

Automatic external defibrillators (AEDs) are used to deliver lifesaving electrical shocks to people with sudden cardiac arrest, a medical condition in which the heart suddenly and unexpectedly stops beating. Defibrillation electrodes are connected to the AED to help the device analyze a patient's heart rhythm and deliver an electrical shock to restore normal heart rhythm when needed.

On Sept. 1, Leonhard Lang sent an "Important Safety Notice" letter to all affected customers. The letter asked customers to:

- Review the safety notice and ensure appropriate staff is aware of the notice.
- Make sure all unused defibrillation electrodes DF29N are secured and destroyed.
- Confirm the products were destroyed by completing the "Confirmation of Destruction / Consumption" form in the notice.
- Send the "Confirmation of Destruction / Consumption" form to their supplier no later than Oct. 14, 2016.

- Keep the signed "Confirmation of Destruction / Consumption" form until their supplier informed them of the termination of this recall.

Health care professionals and consumers with questions are instructed to contact the Leonhard Lang sales staff at (800) 903-6199 with any questions related to this recall.

Read the MedWatch safety alert, including a link to the FDA recall notice, at: http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm525273.htm

Manufacturing

Morocco's Cooper Pharma to build antibiotic manufacturing plant in Rwanda

Cooper Pharma, a Moroccan pharmaceutical maker, has inked a deal to build an antibiotic manufacturing facility in Rwanda, **FiercePharmaManufacturing.com** reported Oct. 25.

The facility would be the first of its kind in the country, a state official told "allAfrica." It is the second such plant construction deal by Cooper, which previously said it signed a deal in Abidjan, Ivory Coast.

The plant in Rwanda is slotted to be built on a nearly 33,000-square-foot plot of land in the Kigalir Special Economic Zone. The facility is expected to open in 2019 and will produce beta-lactam antibiotics, which are among the most commonly prescribed drugs, including penicillins.

The deal, which was designed to help meet local pharmaceutical needs, was announced during a three-day state visit by a Moroccan delegation led by King Mohamed VI.

"The market entry of Cooper Pharma… is in line with the long held wish by the government to have a pharmaceutical plant in Rwanda," Serge Kamuhinda, the COO of the Rwanda Development Board, told allAfrica. "This will reduce our trade deficit and boost exports."

Biocon's Malaysia insulin plant will be ready for commercial production in H2

India's **Biocon** has been working for six years on a massive, $250 million facility to manufacture insulin in Malaysia and says it will soon produce commercial product there, according to the Oct. 21 **FiercePharmaManufacturing.com.**

Biocon Chair Kiran Mazumdar-Shaw made the announcement during an investor call following its earnings release, the "Economic Times" reported. She said the plant will start making Biocon's rh-insulin and insulin analogs for the local market and then move into producing product for export.

"Our facility in Malaysia will be commercialized in the H2 of the current fiscal," Mazumdar-Shaw said.

Biocon says the plant in Nusajaya, which was certified by authorities this year, has 400 employees and represents the largest foreign investment made in Malaysia's biotech sector to date. It also is Biocon's first overseas biopharma manufacturing and research facility.

Biocon began the project in 2010, in part because of infrastructure issues in India that had not been addressed during an economic downturn. Mazumdar-Shaw said at the time that she took the project to Malaysia because the company couldn't be certain of having the power and water needs of a new plant met in India.

The announcement came as Biocon reported significantly higher revenues, up 21% in the Q2 for fiscal 2017 to 992 crore ($148 million), the company reported. Biocon reported improvements in small molecule sales and biologics, but it is in biosimilars where it is drawing lots of attention these days.

In late August, Biocon and partner **Mylan** reported that the European Medicines Agency had accepted their marketing application for the biosimilar version of **Roche's** blockbuster breast cancer drug Herceptin. That put them ahead of rivals there, including **Celltrion**, **Pfizer's Hospira** subsidiary and **Samsung Bioepis**. They are already selling a version in India.

Sterinova opens sterile injectables plant in Canada

Sterinova has opened a $53.3 million ($70 million Canadian) facility in Saint-Hyacinthe in Quebec, having received more than $7 million in funds from public sources, according to the Oct. 19 **FiercePharmaManufacturing.com**.

The 67,000-sq-ft facility will make products in syringes and premix solutions containers. A Sterinova spokeswoman said its first product will be a syringe of the anticoagulant heparin sodium, which she said is the first prefilled syringe of that specific product in the market.

"Sterinova is one of the few pharmaceutical companies in the world to be entirely dedicated to the manufacture of ready-to-use injectable products," Jean-Philippe Gentès, one of the company founders, said in a statement. "Its state of the art technology and its production capacity will make Sterinova an important Canadian player on international markets."

The project received about $5.3 million ($7 million Canadian) from the Quebec Manufacturing Fund and another $1.5 million ($2 million Canadian) from the government of Quebec. The plant was designed with enough space so that its capacity can be doubled, the company said in its announcement. The plant has 55 workers, and another 50 are expected to be added as the company expands. Currently the plant is approved by Health Canada, the company said.

Some of the big players, like **Sandoz** and **Sanofi,** have sterile drug manufacturing in Canada, as well as some smaller operations, like **Jubilant Life Sciences**. Sterile injectables is a hot market right now and there has been considerable M&A action in that field in recent years as more drugmakers develop biologic drugs and contract manufacturers look to cash in on the trend. Last year, for example, Swedish CDMO **Recipharm** agreed to pay $105.2 million to buy a 74% stake in Indian sterile injectables CMO **Nitin Lifesciences.**

Merck KGaA expands Spanish biologics site that produces hot-selling Gonal-f

Merck KGaA, whose sales of fertility drugs have benefited from competitor supply problems, has completed its two-year, €15 million ($16.5 million) expansion of a biologics facility in Tres Cantos, Madrid, Spain, **FiercePharmaManufacturing.com** reported Oct. 18.

According to the web news site, the project boosted the capacity at the facility by 50% and will result in a 20% increase in jobs without providing a precise number. The facility also makes Merck's growth hormone product Saizen.

The 8,000-square-meter (86,111-square-foot) project added 900 square meters (9,687 square feet) of biotech production space and a two-floor office building.

"We are continuously investing in our manufacturing network to maintain state-of-the-art industry level and adapt its capacity to patient needs for our medicines," Thierry Hulot, who heads Merck's global manufacturing and supply for the biopharma, said in a statement. Merck says it has invested €250 million in its manufacturing network this year.

Merck has seen strong sales of Gonal-f. It was a key contributor to Q2 growth, with sales up 23.1% to €209 million, from €177 million in Q2 the year before. Most of that growth came in the U.S., where it benefited from what Merck termed an "advantageous competitive situation."

It gained an advantage after competitors **Ferring Pharmaceutical** in September 2015 recalled 42 lots of its fertility drug Bravelle because of potency concerns. Then last May, the other Merck reported a supply interruption for its ovulation-stimulating hormone Follistim, a supply issue it said it expected to resolve within months.