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FDA: Prepare for Complications When Establishing UDI Systems

BALTIMORE — Devicemakers in the process of setting unique device identification codes with the FDA may want to bake in some extra time, agency officials say.

FDA staff charged with implementing the rule suggest not publishing codes through the UDI system until the device's manufacturing date is solid. That allows extra time for trouble-shooting and making last-minute modifications.

A UDI code that is live in the system cannot be edited, said vocabulary and standards lead Leslie Tompkins, noting that even minor adjustments may require establishing a completely new UDI. And the seven-day "grace period" allows for only a few minor

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Combo Products GMP Guidance Coming Soon, FDA Tells MedCon

CINCINNATI — Manufacturers of combination products can expect draft guidance on current good manufacturing practices in the next several months, staffers in the FDA's Office of Combination Products said May 8.

The guidance will focus on reconciling requirements that differ in the drug and device approval pathways to ensure that products posing similar levels of risk are similarly regulated, even if they're placed in different centers, said OCP Associate Director for Policy John "Barr" Weiner.

"We're not trying to create new regulations. We just want to clarify how to comply with the existing ones," he said, adding the guidance should streamline the process.

He noted, for instance, that regulations on design and purchasing controls and corrective and preventive action only apply

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changes, she added. Tompkins spoke at the three-day UDI Conference 2014.

One mandatory UDI data element is the Global Medical Device Nomenclature, governed by the UK-based GMDN Agency. The vocabulary used by GMDN is shaped by the group's membership and considered to be the only established vocabulary large enough to describe all existing device types, Tompkins said. The breadth of the generic GMDN codes varies by device type, with some terms having more subcategories than others.

The codes make device comparison shopping for patients and caregivers far easier, Tompkins said. The FDA's text-based UDI search database will allow the public to compare features, sizes and recall notifications on a generic type of device, rather than on a specific branded product.

Manufacturers that don't yet have assigned terms need to work with GMDN to select appropriate terms for their device, Tompkins told conference-goers. "If no appropriate terms exist, you may need to build new ones," she said.

Tompkins cautioned that companies with established GMDN terms are not automatically in the clear, because the FDA has decided not to accept terms that have been retired by GMDN. "We understand it's a burden but, on our side, why should we populate a database with data we know is bad?" she asked. "This is the best step for data quality moving forward."

While the GMDN Agency alerts members when it retires a term they are using, nonmember companies are responsible for checking periodically to ensure that they're still using accepted terms, Tompkins said.

None of this is free, and some conference-goers expressed concern about potential costs for small manufacturers.

According to Tompkins, the GMDN Agency charges on a sliding scale based on company size. Charges, which include a set number of device codes, range from $270 to join and $135 each year thereafter for manufacturers with less than $683,000 in yearly sales to about $5,500 and $4,100, respectively, for companies with more than $136 million in sales. Fees for companies with annual revenues greater than $1.3 billion are individually negotiated.

ESG Submissions

Extra time also may be crucial when testing UDI data submissions, said Indira Konduri, program manager of the Global UDI Database. Before initiating tests, manufacturers or parties submitting on their behalf must send a paper letter to the FDA to get what's known as a "letter of nonrepudiation." Once the letter of nonrepudiation is received, the company will name users allowed to upload the data. Manufacturers who have Electronic Submissions Gateway accounts for adverse event reporting or other functions can continue to use that account for UDI submissions, Konduri noted.

Some further delays could occur if manufacturers fail to properly mark UDI files as being intended for CDRH, causing data uploaded to the agencywide ESG to go to the wrong center.

Manufacturers uploading to ESG will get an acknowledgement email for each level of the process, Konduri said. The emails will confirm that ESG accepted the file, that it went to CDRH and that it has been processed by GUDID.

It's not until the final level that any analysis of data quality is performed, Konduri explained. At that time, submitters will get a message telling them whether the data input has passed or failed. In the case of failure, errors will be enumerated, she said.

The UDI final rule, issued in September 2013, mandates that manufacturers imprint a two-part code on a device's packaging or, in some cases, the device itself. The device identifier lists the specific version or model of the device, while the production identifier more precisely identifies the specific device through information like lot/batch, serial number and expiration date. The requirement is being phased in across several years, beginning with Class III devices in September. — Elizabeth Orr

Put Details on OECD Compliance In Conflict Mineral Reports, Expert Says

Lawyers are advising devicemakers preparing conflict mineral reports due to the Securities and Exchange Commission this month to put more effort into describing their compliance with the Organisation for Economic Co-operation and Development's due diligence guidelines.

The OECD guidelines, which most companies are using, lay out five basic steps that companies should follow. But "it's not clear from many [devicemakers'] reports which of those steps, if any, have been followed," says Keir Gumbs of Covington & Burling. "This is one area companies can really focus their disclosure efforts."

Gumbs suggests that devicemakers list the steps and detail their compliance with each one.

Ron Oleynik, a partner with Holland & Knight, agrees that companies should include details on their due diligence programs. While most companies won't have the results of these efforts when they file their report, they can show they are working through the process systematically.

This could include forming a group, setting out a methodology and coming up with a work plan, he says. "That, at this point, is going to be the key to putting together a conflict minerals report."

No SEC Stay

Some companies may have been hoping for an SEC stay of the rule after last month's decision by the U.S. Court of Appeals for the District of Columbia Circuit that certain provisions violated the First Amendment.

While this created some uncertainty about the rule's immediate fate, the SEC chose not to stay the rule and, on May 14, the D.C. Circuit Court rejected a motion for a per curiam review of the decision, Gumbs says. This means the requirements will remain intact at least until initial reports are due in June.

"Even the most optimistic estimates would put any district court action well after June at this point," he says.

As devicemakers prepare their reports, Gumbs warned that the form they must fill out is not entirely clear and can be misunderstood, leading to failure to complete all the form requirements. For example, the form requires identification of the product, "but on a number of examples, companies haven't identified the product and sometimes haven't even provided the categories of product," he tells *GMP*.

Uncertainties Remain

While devicemakers face consequences for not submitting a report, it's unclear what the consequences may be for submitting a "bad report," Gumbs says. "Some companies, I think, are going to be fairly cavalier, and the question is: Is the SEC going to issue comments or bring enforcement action, and are activists going to get involved?"

There are additional uncertainties around how much devicemakers are going to disclose about the results of their due diligence, since disclosing conflict status is voluntary.

While consumer-facing companies are expected to disclose their status, "for medical device companies, I think it's a little bit less certain because I don't think there will be any benefit that they can expect to get," Gumbs says. The reports that Covington & Burling has seen so far are "all over the place," in this regard, he adds. Some companies included their conclusion and some did not, "but everyone is looking to see what everyone else is doing."

Companies also have questions about how much detail on their processes is enough, or possibly too much, he says. "We've seen a fairly wide range of disclosure, ranging from four or five pages up to 14. It's hard to see where things are going to shake out for most companies."
— April Hollis

FDA's QS Device Inspections, Warnings Increased in 2012

Routine quality system surveillance inspections of foreign devicemakers increased by 93 percent in 2012, according to newly released FDA data. Overall QS inspections were up 37 percent for the year.

The number of warning letters also rose that year, due to "an increase in inspections, increased focus on foreign firms by the foreign device cadre and improved site selection," the agency says. However, there were fewer "official action indicated" inspections that resulted in untitled letters because of missed FDA deadlines or insufficient evidence.

Foreign companies accounted for 300 — or 10 percent — of the FDA's 2,748 QS inspections in 2012. They also accounted for 62 (32 percent) of the 195 OAI outcomes and 66 (40 percent) of the 164 warning letters.

CAPA issues, along with inadequate production and process controls, topped the quality issues FDA investigators found in 2012. Both observations were noted in 30 percent of Form 483s.

Other frequent observations related to quality audits and complaint files, specifically establishing and maintaining procedures for receiving, reviewing and evaluating complaints. Additionally, "the number of observations related to … device history record increased significantly in 2012," the FDA says.

For warning letters, problems with CAPA procedures and complaint files were the most frequent citations. The agency notes two violations that were cited at higher rates in warning letters than in inspectional observations:

- Fifty-one letters included a design history documentation violation; and
- Forty-nine letters included a process validation violation.

Of 164 warning letters with QS citations, 32 percent included CAPA citations, 30 percent cited production and process controls, 16 percent cited design controls, 12 percent involved documentation controls and 10 percent cited management controls.

View the FDA's 2012 quality systems data at www.fdanews.com/ext/resources/files/05/05-07-14-inspectiondata.pdf. — April Hollis

FDA Warns Cook Over Uncleared Design Changes

Cook Vascular was handed an FDA warning letter for marketing the Cook Evolution RL and the Shortie RL Bi-directional Dilator Sheath Sets without marketing clearance or approval.

The agency reviewed Cook's website and found promotional material indicating the Cook Evolution Mechanical Dilator Sheath Set has undergone design changes since its clearance, according to the April 15 letter posted recently online. These changes include "what appears to be an extension to the Evolution line and material changes to the sheath," the letter says. The device is cleared for use in the percutaneous dilation of tissue surrounding cardiac leads, indwelling catheters and foreign objects.

Meanwhile, a brochure for the Evolution RL lead extraction system makes claims that the device's clearance doesn't support.

The brochure advertises that it has a decagon-shaped tip, a birotational sheath and can rotate in alternating directions or continuously in either direction. But "the cleared birotational sheath does not provide a mechanism for changing the rotational direction or have a decagon-shaped tip," the letter says. "It only cuts tissue when rotating clockwise."

Cook has also updated the handling system and is offering larger-sized sheaths than described for the original cleared system, the letter notes. A larger size could bring new risk factors.

Cook did not respond to a request for comment by press time. View the warning letter at www.fdanews.com/ext/resources/files/05/05-06-14-Cook.pdf. — April Hollis

FORM 483 INSIDER

Irish Devicemaker's 483 Notes Rusty Tables in Clean Room

Natus Manufacturing Limited, an Irish devicemaker, received an FDA Form 483 for slips related to acceptance activities and contamination-prevention procedures.

The FDA investigator observed rusty tables, cabinets and other equipment in the company's clean room near the packaging area. The automated needle electrode assembly machine had "chipped paint all around its surface," according to the Jan. 23 form, recently released.

Natus also had multiple air microbial failures in the clean room in 2013 and in 2012, the form says.

In a second observation, the FDA notes Natus lacked statistical rationale to justify its sampling method for acceptance activities, including in-process inspection and finished device inspection for needle electrodes.

Natus did not respond to a request for comment by press time. The Form 483 is available at www.fdanews.com/ext/resources/files/06/06-04-14-Natus.pdf.

South Korean Needle Maker Gets 483 After Stacking Needle Bins

During an FDA inspection, an employee of Precision Needle Manufacturing placed a bin of needle protectors on the ground and then later stacked the same bin on top of another container with exposed needle protectors, according to a Form 483.

This action was taken in the manufacturing area where sterile and nonsterile products, including spinal needles and epidural needles, are assembled, according to the Jan. 9 form, which was recently released.

The South Korean manufacturer also failed to outline in its purchasing procedure the actions that should be taken when a category 2 supplier falls short of the minimum overall quality score. "One category 2 supplier did not meet the … score yet no action was taken by the inspected firm," the form says.

Meanwhile, no supplier audit was conducted for a category 2 supplier in 2012, and the company's purchasing procedure did not specify the frequency of supplier audits.

Out of three CAPA files reviewed, none included documentation of root cause investigations. Precision's CAPA procedure lacked requirements for verifying and validating CAPAs and for implementing and recording necessary changes.

Three of five nonconforming records reviewed by the FDA investigator did not adequately record the disposition of nonconforming product after sorting activities, and one did not record the justification for use of nonconforming product.

None of the five complaint records reviewed had all of the documentation required by the company's procedure. They lacked dates and results of the investigation, corrective actions taken and replies to the complainant.

Precision could not be reached for comment by press time. The Form 483 is available at www.fdanews.com/ext/resources/files/06/06-04-14-Precision.pdf.

Moeller Medical Gets 483 For Procedural Issues

German devicemaker Moeller Medical received an FDA Form 483 for procedural failures related to suppliers, testing and design changes.

The company's supplier procedures lack provisions requiring suppliers to notify it about changes in product or services if the suppliers are not currently under a quality agreement with Moeller, the form says.

Another observation relates to bioburden testing, which is required yearly for tube sets used with the company's LiquoGuard product. Despite this requirement, no identification of bioburden

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Hospira Recalls Infusion Pumps, Docking Station for Pumps

Hospira's troubled infusion operations faced another setback with the announcement last month of two recall actions.

The Lake Forest, Ill.-based company alerted customers May 2 that its GemStar Docking Station, which is used with the GemStar infusion pump, may cause a pump to fail to power up. And when used in conjunction with a battery pack, the pump sometimes detects excess power and issues an alarm. Either error could result in a delay in therapy.

In lieu of returning the docking stations, Hospira suggests turning the pump on and removing the battery pack before plugging it into the docking station.

The products have been in distribution since 2002. In 2013, Hospira announced it was retiring the product line and will cease formally supporting the docking stations on July 31, 2015.

Broken Door Assemblies

Hospira also announced a voluntary Class I recall of Abbott Acclaim infusion pumps and Hospira Acclaim Encore infusion pumps due to customer reports of broken door assemblies. The door helps assure that the tubing is sealed properly to ensure appropriate flow of therapy to the patient. A door that doesn't close properly could cause an over-infusion or delay of therapy, the company said.

The affected pumps were manufactured and distributed between February 1997 and November 2013. The company is asking customers to inspect all pumps in use for door cracks and retire from service any that are found to be defective.

Hospira has faced a slew of regulatory problems in recent years.

In April, the company withdrew an anesthetic after steel particles were detected in the solution. And in March, the company's Rocky Mount, N.C., plant received a warning letter complaining that its corrective and preventive action procedures for devices fall short of expectations — the second warning letter the plant had received since 2010 (*GMP*, April).

The company did not respond to a request for comment on the latest quality issues.
— Elizabeth Orr

Combo Guidance, *from Page 1*

to devices, while drug rules cover calculation of yield, tamper-evident packaging and reserve samples. The agency welcomes input on cGMP issues for combo products, though Weiner noted it may be too late for comments to be reflected in the draft guidance.

Weiner believes the FDA is "getting better and better" in terms of consistency, but says discrepancies in the drug and device approval processes, and in enforcement, remain. He spoke with other OCP staff at the FDA/Xavier University MedCon conference.

Other current OCP priorities include developing draft guidance on human factors in clinical trials of drug-device combos, issuing a final rule on postmarket safety, updating aging inter-center agreements and starting work on draft guidance on humanitarian use device/humanitarian device exemption policies for combination products, said OCP Director Thinh Nguyen.

In 2013, OCP reviewed 106 new products. Seventeen were combination products, 14 were not and three were bounced because they were not actually FDA-regulated — a first, Nguyen said. Another 72 submissions lacked information and remain under review. The office also offered advice in 230 formal consultations from other FDA centers and 390 requests about premarket review from FDA staff or product sponsors.

"The number of approved products may look low," Nguyen said, "but we're definitely busy."

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Industry Still Waiting on Details Of UDI Enforcement, Expert Says

CINCINNATI — With September's deadline for displaying unique device identifiers on high-risk devices just around the corner, rollout for many manufacturers is well underway. Yet questions remain about how the FDA will enforce the new requirements, says Steve Niedelman, an FDA veteran and lead quality and systems consultant at King & Spalding.

Under the UDI final rule, manufacturers are required to imprint a two-part code on a device's packaging or, in some cases, the device itself. The device identifier lists the specific version or model of the device, while the production identifier more precisely identifies the specific device through information like lot/batch, serial number or expiration date. The company must submit all of that information to the FDA's Global Unique Device Identification Database.

But the FDA has yet to explain how UDIs will be considered in the context of device enforcement, Niedelman told a May 7 session of the FDA/Xavier University MedCon conference. For example, will UDI violations be reported on Form 483s after inspections? And will warehoused devices returned due to lack of a UDI after several years in storage be considered a reportable recall?

And while manufacturers must create a new UDI any time there is a new version or model of a device, it isn't clear whether reviewers will look at the proposed UDI when they're considering a device for approval or 510(k) clearance, Niedelman said. "There's no official relationship to premarket approval, but it's certainly going to be considered during premarket enforcement," he added.

Niedelman noted that manufacturers of Class III devices can seek a one-year extension for displaying UDIs, but the request must be made by the end of June.

Exemption from UDI is possible, Niedelman said, but the FDA's threshold for exemption is "rather high," and the agency may rescind a waiver at any time. The FDA will list UDI-exempt products on its website.

To help prevent a backlog, the FDA is advising companies that obtain an exemption on one product and have others that may qualify on similar grounds to assume the exemption applies to those products as well, Niedelman said.

Devices intended for multiple uses, or for reprocessing, should be directly marked with UDIs, Niedelman advised conference-goers. However, reprocessors are not required to add new UDIs to refurbished devices. Devices that cannot be marked with UDIs due to technical or safety factors also are exempt, he said.

"If you have an exemption, just document it in the design history file," Niedelman said. "The FDA doesn't need to be notified."

Medical Apps

Niedelman had tips for manufacturers of medical apps as well. For software regulated as a medical device, the UDI should be displayed either when the program opens or as a pop-up window. Software sold on store shelves should also include a UDI on the packaging, he said.

Any time a new version of the software is introduced, the manufacturer will need to create a new UDI. If the change affects safety, the lot number should be altered. For cosmetic modifications and minor bug fixes, a new production identifier should be sufficient, Niedelman said.

UDI requirements for devices sold in multi-unit packages are another source of confusion, the consultant said.

For instance, a manufacturer selling a box of 10 bandages does not need to display the UDI on each individual bandage. But when the manufacturer uploads data about its products to the UDI database, each bandage must be noted. "Even though each bandage is not labeled, it must exist in the UDI database," Niedelman said.

He added that combination products that carry New Drug Codes are exempt from UDI requirements. However, combination device components not covered by an NDC must bear a separate UDI. — Elizabeth Orr

Work on Device Quality Database Starts Later This Year: Silverman

CINCINNATI — CDRH's Office of Compliance expects to begin work on a public database of device quality information, such as MDR reports, by the end of the year, OC Director Steven Silverman told devicemakers May 7 at the FDA/Xavier University MedCon conference.

While systems within the agency allow regulators to easily view and manipulate data on device quality, that's not the case with outward-facing systems, Silverman said.

Funding problems have kept a solution off the table for years, but he now anticipates development work will begin this year.

Silverman emphasized that the number and causes of Form 483 reports and warning letters have not changed significantly in several years.

"The question is: Are we being effective?" he said.

"Our goal is not to issue warning letters," he told conference-goers. "Our goal is to support compliance. If violations are the same year after year, we may not be succeeding."

To counter those problems, CDRH has implemented an internal Case for Quality policy, which argues that company-wide incorporation of quality standards is more effective than a more localized effort.

The center has also launched the Voluntary Compliance Improvement Program, which allows manufacturers with repeated quality violations to seek extra help from the FDA to remedy their problems.

Initially, the program will have just three to five participants, but Silverman expects it to expand if successful.

Office of Compliance staff also are working to schedule more frequent educational sessions for industry to spread the compliance and quality message, he said. — Elizabeth Orr

CooperVision Cited for Investigations; FDA Requests Staff Training

CooperVision's Puerto Rico facility has received an FDA warning letter for inadequate investigations into nonconformities and other GMP issues. While the company will need to improve staff training, the letter should not hurt operations or approvals, an analyst says.

According to the Feb. 27 letter, the contact lens maker's corrective and preventive action investigations did not evaluate the impact of reported problems on the affected device, or on affected products in commercial distribution. The company also lacked interim controls to implement while corrective actions were in progress, the letter says. The letter, which followed a Dec. 10, 2013, to Jan. 10 inspection by the FDA's San Juan district office, was recently posted on the agency's website.

Another CAPA investigation followed complaints about power failures for distributed Pro-Clear One Day lenses. The company confirmed the complaints and found that devices were released for distribution while not in compliance with the labeled power specification. "We are concerned when a firm uses the product's end-user as quality control based on use discomfort resulting in visual acuity disturbance," the letter says.

While the warning letter will necessitate better staff training, it is unlikely to require significant spending or lead to any product recalls, says Wells Fargo analyst Larry Biegelsen. He notes the training "could take some time to execute," but the company expects to be ready for reinspection within the next two months.

CooperVision "has already responded to many of the violations in the WL and much of the remaining outstanding issues are administrative in nature," Biegelsen says. "The bottom-line is that the WL is unlikely to affect ongoing plant operations or potential new product approvals."

In addition to problems with investigations, the FDA cites timeliness issues with a December 2011 CAPA related to metallic particles found during in-process testing of lenses. "We find it objectionable that containment activities were not implemented until October 2012, and the risk assessment was not finalized until 09/13/13," the letter says. "This CAPA was closed on 09/16/13, without revising the FMEA addressing the presence of particulate matter, categorized as a 'minor' defect."

CooperVision also failed to justify its categorization of the defect as minor and did not conduct a scientific assessment of the defect for devices in commercial distribution, the letter notes. The FDA raises concerns with CooperVision's defects classification system and recommends reassessment of the company's controls for establishing and classifying product defects.

While the company's postinspection response indicated that no complaints had been reported for the particulate issue, the FDA points out that metallic particles could still be present in distributed devices due to ineffective corrective actions. "Bear in mind that your current in-process controls might allow for the release of devices with particulate matter without requiring the identification of particulate matter as part of your investigation," the letter says.

Another CAPA investigation into particulate matter in products distributed in Japan was not extended to other devices that shared the same raw materials and manufacturing equipment, according to the letter. These devices were distributed to the U.S. market.

The FDA investigator also reviewed CooperVision's CAPA SOP, finding it lacked timeframes for completing investigations based on a revised risk classification, implementing subsequent corrective and preventive actions and verifying effectiveness. "It also failed to provide specific instructions for conducting risk assessments, Health Hazard Evaluations, and the containment of product when the criticality of the problem merits due diligence," the letter says.

CooperVision did not respond to a request for comment by press time. The warning letter is at www.fdanews.com/ext/resources/files/05/05-20-14-CooperWL.pdf. — April Hollis

FDA Workshop to Discuss Controls for 3D Printing

As 3D printing gains popularity among medical devicemakers, the FDA wants to get advice from manufacturers and researchers to guide its product reviews and, possibly, future guidance.

The technology is just beginning to enter mainstream use in medical technology, according to a May 19 *Federal Register* notice. "FDA has begun to receive submissions using additive manufacturing for both traditional and patient-matched devices, and we see many more on the horizon," the FDA says. "Industry forecasts project significant growth of additive manufacturing in both traditional and innovative environments by 2025."

Patient-specific devices and devices with internal complexity/porosity have been common candidates for 3D printing, FDA spokeswoman Susan Laine told *GMP*. "Generally, products challenging to make using traditional manufacturing are also good candidates for 3D printing."

Laine said CDRH has cleared a number of 3D-printed devices via the 510(k) pathway. And "a search of biomedical journal publications shows an increasing trend of 3D printing research," she said. "Coupled with the increasing availability of 3D printers, we expect that interest in 3D printing will continue to grow."

To prepare for this upsurge, the agency is planning a public workshop this fall to discuss technical considerations and challenges of the technology. In particular, the agency seeks "input regarding technical assessments that should be considered for additively manufactured devices to provide a transparent evaluation process for future submissions."

Ideas and advice from the workshop may help the agency create new draft guidance or standards for additive manufacturing of medical devices, the notice says.

According to the FDA, 3D printing can aid in the production of device structures and features that used to be impractical or impossible to manufacture. Companies already use 3D printing as an alternative means of creating traditional components and patient-matched devices. "As the technology matures, additional capabilities may be incorporated into medical devices," the agency says.

3D printing also allows designers to make quick changes to products to create new prototypes and to produce small batches of different product designs. It is when devices are produced individually or in tiny batches, however, that process verification and validation are most important, the FDA says.

In addition to validation and verification, the meeting will cover material chemistry, physical properties, recyclability, part reproducibility, post-processing steps, software, cleaning and effect of complexity on sterilization and biocompatibility.

The meeting is slated for Oct. 8 and 9, from 8 a.m. to 5 p.m., at the FDA's White Oak campus in Silver Spring, Md. See the *Federal Register* notice at www.fdanews.com/ext/resources/files/05/05-19-14-3-D.pdf. — April Hollis

Design, Process Validation Lead to Warning for Acme

Acme Monaco received an FDA warning letter for failures related to design validation, process validation and other GMP issues.

According to the April 28 letter posted recently online, the company did not validate the design of its polytetrafluoroethylene-coated guidewires under actual or simulated conditions for use. Further, its risk analysis is inadequate because it doesn't assess flaking and delaminating of the coating during use.

The New Britain, Conn., company, which makes guidewires for cardiovascular and urologic use, also lacks procedures to control changes to the device design, the letter says. Acme changed the formulation of the PTFE coating material "without any evaluation of validation, verification, review or approval prior to implementation of the change."

According to the letter, Acme did not validate the following processes:

- Cleaning of finished medical guidewires before coating using the Ultra Kool vapor immersion type solvent-based degreasing unit;
- Post-coating of guidewires it contracts to outside vendors; and
- Solvent-based cleaning of precoated guidewires using equipment designed and built by the company.

Corrective action slips also drew FDA scrutiny. The company did not implement identified corrective actions in response to a complaint about PTFE coating flaking during use. "You identified the need for an acceptance test to assess coating integrity for incoming coated guide wires received from outside vendors on 8/7/13, but did not implement action prior to shipping product from lot 056066-1-1A on 8/23/13 or lot 056066-1-1B on 10/3/13," the letter says.

The company also failed to adequately investigate nonconforming product so it could identify all appropriate corrective actions.

For example, Acme identified nonconforming product in the inventory of one lot of guidewires that had been shipped. Out of 1,680 guidewires, 1,010 failed wet abrasion and tape tests for flaking coating and bent or bridging parts. But the investigation did not include a risk assessment to identify any health hazard associated with the distributed units, which did not undergo acceptance testing for coating integrity.

Acme did not respond to a request for comment by press time. The warning letter is available at www.fdanews.com/ext/resources/files/05/05-06-14-Acme.pdf. — April Hollis

Argentina Sets Medtech Traceability Requirement

Argentina's ANMAT has adopted strict traceability requirements for medical devices, with the aim of stemming the flow of counterfeit products.

The system — similar to one already in place for pharmaceuticals — will be implemented in two stages. Manufacturers and distributors of implantable cardioverter defibrillators, cochlear implants, intraocular lenses, pacemakers and breast implants, or their legal representatives, must comply with the traceability scheme by Oct. 23. The deadline for coronary stents, hip replacements and trauma products is April 23, 2015.

Devicemakers should place the following information on the device packaging:

- Global trade item number;
- Serial number up to 20 alphanumerical characters;
- Lot; and
- Expiration date in DD/MM/YY format.

Marketing authorization holders, distributors and healthcare facilities where a device is implanted should register in ANMAT's National Medical Device Traceability System Database. They should also have hardware and software to track device movements. Any participant in the

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organisms is required by company procedure or included on yearly test results, according to the Jan. 30 form, recently made available.

Meanwhile, the company's procedure and template for design changes and change requests do not require documentation of the decision on whether a change requires validation. "There is no procedure requiring that design validation be performed using production units or their equivalents, and design validation documentation does not contain information requiring or verifying that production units were used," the form says.

Moeller did not respond to a request for comment by press time. The Form 483 is available at www.fdanews.com/ext/resources/files/06/06-04-14-MoellerMedical.pdf.

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Of the 17 designated combination products, 14 were drug/device, two were biologic/device and one was a drug/biologic. As in most years, slightly more than half of submissions went to the FDA's drug center, with the remainder split between CDRH and the biologics center. The number of products assigned to CDRH peaked at 28 in 2010 and has been declining since, Nguyen said.

Most combination products are surprisingly similar, Nguyen said. "Every so often, we'll see something I would consider truly innovative, but mostly what we get is that someone takes a device and adds a drug to it." — Elizabeth Orr

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supply chain that does not implement a traceability system won't be allowed to continue making, importing, distributing or implanting devices, the agency says.

Fernanda Machado, associate vice president for global strategy and analysis at AdvaMed, says that while the traceability system may present challenges to local distributors, multinational devicemakers shouldn't have a problem. "There will be some costs, it will take some time to adjust, but it should be fairly easy," she tells *GMP*.

Argentina's scheme will be similar to ones elsewhere in Latin America, such as Brazil, Machado says. "I don't know if ANMAT has the same capability as ANVISA … but I'm not really concerned because I know that they have some [quality] staff they can probably relocate to this program," she adds.

Doctors also play a role in the traceability scheme, having to record implantations in the database, Machado said. She expects ANMAT will eventually involve medical associations and work with hospitals as is done in Brazil, where devices are tracked by serial number.

While the system initially applies only to implantable devices, Machado believes it will be expanded to all medtech products. "It's all about safety and about patients," she said.

View the traceability system in Spanish at www.fdanews.com/ext/resources/files/05/05-14-ANMAT.pdf. — Meg Bryant

FDANEWS

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Right the First Time
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In certain situations, it may not be obvious what the right thing is, but this 14-minute video presentation addresses potentially sticky issues such as:

- How to identify subtle pressures that lead to unethical behaviors
- How to respond when asked to behave unethically
- How to handle awkward situations involving ethical dilemmas
- The importance of doing the right thing the first time
- And much more

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Supplier Qualification:
Developing Risk Assessments and Audit Programs That Work

The FDA is drafting tough new drug GMP standards ... targeting devicemakers with Warning Letters for inadequate supplier qualification and process documentation ... even notifying companies directly when it finds their suppliers are not complying with GMP.

Here's how to sort out the regulatory requirements for auditing suppliers in a sensible way that will protect both your products — and your budget. You can tighten up your auditing process and keep the FDA out of your hair. ***Supplier Qualification: Developing Risk Assessments and Audit Programs That Work*** will show you how.

It's a real-world approach on how to design an audit program that works, and is also practical and sustainable. You'll discover how to balance major factors that underlie more effective audits — scheduling, selecting auditors, determining when to use outside auditing help, and building an audit program that passes muster with the FDA and other regulators.

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