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FDA Adds Device Scenarios to Final GMP Guidance for Combo Products

The FDA finalized guidance on GMP requirements for combination product manufacturers, adding scenarios to clarify how to comply with certain device requirements.

The 59-page guidance — which covers GMP requirements for drug-drug, drug-device, drug-biologic and biologic-device combination products — is largely identical to the 2015 draft guidance, except for the addition of compliance examples for prefilled syringes, drug-coated mesh and drug-eluting stents.

When a manufacturer intends to apply for marketing approval for a prefilled syringe of a previously approved drug product, the manufacturer must demonstrate compliance with both the drug GMPs and device quality system regulations, the guidance said.

The manufacturer must ensure that its system fully complies with the drug GMPs for this product, taking into account all of the issues raised by inclusion of the device constituent part — including

(See **Combo Products**, *Page 2)*

FDA Clarifies IDE Risk-Benefit Assessment

The FDA has released final guidance on assessing the risks and benefits of investigational device exemption (IDE) applications for human clinical studies.

Assessments must include an analysis of all incremental risks to which patients will be exposed by the investigation, as well as how the risks will be minimized. Specific factors include:

- The type of risk, such as physical safety, serious injury or illness, procedure-related complications, risks of the study itself, and false positives or false negatives for diagnostic devices;
- The likelihood of the risk;
- The duration of the risk; and

(See **IDE**, *Page 4)*

Customer Services Assoc. Hit With Form 483 for Procedures

Customer Services Associates received a Form 483 for not developing written medical device reporting procedures, establishing procedures for corrective actions and reviewing complaints, and other violations.

During an October inspection of the company's Winchester, Ind., facility, inspectors found that Customer Services had not developed and maintained written MDR procedures. Specifically, there were no procedures for identifying, communicating, and evaluating events that maybe subject to MDR requirements; timely transmitting complete MDRs to the FDA; and keeping appropriate records.

The inspectors also found that Customer Services Associates had not established corrective and preventive action (CAPA) procedures, including ones that specified when quality issues would result in CAPA actions. For example, between May 2014 and September 2016, the firm received 76 complaints related to its blood pressure monitoring kiosk. Thirty of these complaints were attributed to a cuff leak, but further investigation of the root cause was not elevated to a CAPA.

The company also failed to document labeling inspections for blood pressure kiosks, including inspections for accuracy and final release of the labels. Additional violations included an inadequate device record, failure to specify where rework activities and subsequent inspection were documented, and failure to maintain records that justified not reporting a correction and removal action to the FDA.

Read the Form 483 here: www.fdanews.com/01-05-17-CustomerServices.pdf.

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management responsibility, design controls, verification and changes, as well as risk analysis.

Meanwhile, the guidance's drug-eluting stent scenario considers four separate manufacturers: the owner of the stent; the maker of the active pharmaceutical ingredient; the manufacturer of the polymer used to bind the bulk drug substance coating to the stent; and the company producing the primary packaging.

Because the owner of the stent is purchasing the other three, it is up to the owner to make sure the other products approved for use.

The final version reiterates that combination product makers have two options for compliance: satisfy all drug and device GMPs, or implement a streamlined quality system that focuses primarily on one but incorporates elements of the other. Like the draft, the final guidance details which GMPs are applicable to a product, general methods for how to implement them, key definitions, and how to make postmarket changes to a product's quality system. These recommendations have not changed.

In comments on the January 2015 draft guidance, Advamed said it was encouraged that FDA devised a streamlined program intended to assist manufacturers in complying with 21 C.F.R. Part 4. However, it asked for additional clarification on how best manufacturers can comply with this regulation.

The FDA advised manufacturers to contact the lead center for their product, either CDRH, CDER, CBER, or the agency's Office of Combination Products, if they have questions on GMP compliance.

The final guidance is available here: www.fdanews.com/01-11-17-FinalGuidance.pdf.
— Derek Major

UK's MHRA Issues Alerts For Glucofacts Software, X-ray Systems

The UK's Medicines and Healthcare products Regulatory Agency (MHRA) has issued a safety alert based on a notice issued by Ascensia Diabetes Care Holdings.

Ascensia said its Glucofacts Deluxe software for the Contour Next/Plus One blood glucose meter may give inaccurate readings when users enter insulin and carbohydrate values in the Contour Diabetes app in conjunction with version 3.10.07 of the software.

Read the notice here: www.fdanews.com/01-05-17-Ascensia.pdf.

China's Fast Track for Innovative Medical Device Approvals

Grace Fu Palma, founder and CEO of Boston-based China Med Device, a firm specializing in commercialization and funding for medtech companies entering China, explains how medtech companies can use a new guideline from the China FDA to help secure fast track approvals for innovative medical devices.

CFDA issued a new guideline for document preparation of innovative medical device special approval process on Dec. 15, 2016. The initial general decree that governs the general requirements of innovation approval was first issued on Feb. 7, 2014. Since then, a series of documents have spelled out the reviewing and feedback process. CFDA gained more experience in the past 2 years after more than 400 products have been submitted.

This new guideline provides more details to regulate the preparation and writing of documents for the special approval of innovative medical device. There are some important parts of the new guideline for foreign medtech companies who want to gain faster access to China market:

1. Foreign (such as U.S.) medtech companies can also apply for this fast track special approval for innovative medical devices if the foreign companies meet the following requirements (For details, please refer to the Feb 7, 2014 decree).
   a. **Patent.** The product should have a patent in China. You do not need to wait for the final patent approval to claim your qualification. If you have received the public notice for verification from the China patent office, you can be qualified. Furthermore, the patent does not need to be originated in China. If an entity in China is licensed with the usage or ownership rights of the patent, you can qualify. Therefore, when you apply for new patents and value China medtech market, make sure that you have China PTO coverage.
   b. **Innovation and clinical significance.** The guideline spelled out what types of documents are needed to demonstrate that your medical device will meet this requirement. The product must have significant clinical application value and improvement over the current products in the categories claimed both in China and globally.
   c. **Prototype product.** The applicant should have completed the preliminary study of the product and have a prototyped product.
2. Once you get the "innovative medical device" designation, you can be put on the fast track with a designated CFDA reviewer and priority status for fast track approval.
3. The documents required to submit include: 1) Application form; 2) Business Legal Agent certificate; 3) Product intellectual property rights certificate; 4) Overview of product development process and results; 5) Product technical documents; 6) Documentary evidence of product innovation; 7) Product safety risk management report; 8) Instructions for use; 9) Other documents relate to product intellectual property; 10) Agent related information; and 11) Declaration of Authenticity.
4. Applicant should also submit electronic documents.

The guide provides the details of the required submission documents and their formats.

In summary, U.S. or other foreign companies as well as Chinese medtech companies are eligible to use these guidelines to see if they are qualified and to prepare the necessary documents to gain a fast track to CFDA approval.

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Editor's Note: Grace Fu Palma will be presenting an FDAnews webinar titled **China Medical Device Regulatory Changes** on Jan. 31. See details here: www.fdanews.com/chinamdregulatorychanges.

FDA Lays Out Possible LDT Oversight Approach

After spending months analyzing more than 300 comments on its draft laboratory developed test guidance, the FDA yesterday punted the issue to allow more public discussion and a possible legislative solution rather than making the controversial guidance final.

In a discussion paper, the FDA outlined a possible approach that would focus on new and significantly modified high- and moderate-risk LDTs.

The FDA acknowledges that there is a growing consensus that additional oversight of LDTs is needed, as reflected in several proposals from organizations representing laboratories and the IVD industry. Although the proposals differ in some respects, they generally share the following features:

- A risk-based approach to oversight;
- Independent premarket review for certain tests and for some modified tests;
- A focus on analytical and clinical validity as the basis for test approval;
- Risk classification activities;
- Adverse event reporting;
- Exemption of certain categories of tests from premarket review;
- A robust laboratory quality system;
- "Grandfathering" for tests available prior to a specific date; and
- Public availability of test performance information.

But these proposals differ with respect to which federal agency would be responsible for any additional oversight: the FDA, the Clinical Laboratory Improvement Amendments, which is overseen by CMS or a hybrid model under which FDA and CMS share oversight.

The shared model, according to the FDA, is supported by more stakeholders than the other options according to feedback it received.

The FDA also lays out several alternatives to what it proposed in 2014, including:

- Exempting LDTs already on the market from all FDA oversight except for adverse event and malfunction reporting ("grandfathering"), and exempting traditional LDTs and LDTs for public health surveillance from all oversight;
- Not adopting proposals requesting laboratories to notify FDA of their LDTs on the market because FDA generally would no longer need to classify LDTs currently on the market as the result of "grandfathering";
- Providing additional time before FDA would begin actively overseeing certain regulatory requirements; and
- Shortening the overall phased-in timeframe.

Read the discussion paper here: www.fdanews.com/01-13-17-LDTs.pdf

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- Possible risk-mitigation approaches.

The assessment of benefits should focus on concrete rather than hypothetical benefits and should include:

- The type of benefit, such as the device's anticipated impact on health or clinical management;
- The magnitude of the benefit;
- The likelihood of participants experiencing a benefit; and
- The duration of the effects.

Risks and benefits to healthcare workers and others involved with the study also should be considered, as well as interpretive risks such as the likelihood of drawing false conclusions from the data.

The final guidance is similar to draft guidance issued in June 2015 but clarifies that the FDA will not disapprove an IDE based on study design. However, it does state that well-designed studies are more likely to produce important knowledge about a device or disease, and poorly designed studies can lead to false conclusions.

Read the final guidance here: www.fdanews.com/01-12-17-IDEguidance.pdf.

FDA, DHS Warn of Cyber Vulnerabilities In St. Jude Cardiac Devices

The FDA and the Department of Homeland Security have flagged cybersecurity weaknesses in some St. Jude Medical implantable cardiac devices used with the company's Merlin@home transmitters.

The two federal authorities said the systems can be vulnerable to attack, especially as medical devices become increasingly interconnected via the Internet, hospital networks, other medical devices, and smartphones. By reconfiguring the transmitter, it is possible for a hacker to remotely access a patient's device and cause inappropriate pacing or shocks.

St. Jude released an automated software patch for the transmitter on Monday. The FDA said the benefits to patients from continued use of the device outweigh the cybersecurity risks.

The FDA notice is available here: http://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/ucm535843.htm.

The DHS notice is available here: https://ics-cert.us-cert.gov/advisories/ICSMA-17-009-01.

CFDA Issues Guidance on Quality Control, Product Inspection

The China Food and Drug Administration (CFDA) has issued new guidance on quality control, finished product inspection, and other procedures for medical devices.

The document focuses on purchase control, process control, and finished product inspection — and includes a catch-all section on "other relevant requirements."

The section on purchase control requires manufacturers to implement specific procurement control procedures. Raw materials and components that have a greater impact on the quality of finished goods must adhere to more rigorous standards. Inspection procedures for incoming goods must specify acceptance criteria, test methods, sampling procedures, and other information.

The process control and inspection section establishes similar rules for intermediate products and production processes. Manufacturers should consider how computer software affects product functionality when establishing quality control processes, the CDFA says.

The third section sets criteria for finished product inspection, including required processes, label inspections, and related tasks.

The final section on other relevant requirements addresses procedures for monitoring fluctuations in product quality and the ability to meet production demands. — Jeff Kinney

Swissmedic Grants Grace Period For Orphaned Manufacturers

The Swiss Agency for Therapeutic Products (Swissmedic) announced that it will allow orphaned manufacturers whose Notified Bodies have ceased operation to continue marketing their devices, subject to certain conditions.

EU regulators are implementing stop-gap measures to ensure continued access to the EU market for medical devices with EC certificates granted by Notified Bodies that are no longer operating due to more stringent requirements under the European Medical Device Regulations. The Swissmedic announcement follows a similar announcement by France's National Agency for the Safety of Medicines and Health Products (*IDDM*, Nov. 23, 2016).

Swissmedic said that for up to 12 months following the partial or complete de-designation of their former Notified Bodies, manufacturers may continue to market devices bearing the identification number of the previous Notified Body if product safety is ensured and a new Notified Body has begun renewing the CE certificate.

The number of qualified Notified Bodies has dropped from more than 80 to fewer than 60, and is expected to decrease even more, Swissmedic said. This has led to about 3,000 EC certificates not being monitored by a Notified Body.

Acumedia Manufacturers Cited For CAPA, Other Procedures

Acumedia Manufacturers was cited in a Form 483 for inadequate corrective and preventive action (CAPA) procedures, failing to report a correction or removal, and other violations.

Following a visit to Acumedia's Lansing, Mich., facility in late September and early October, inspectors reported that the firm failed to analyze all quality data sources to identify existing and potential causes of nonconforming product or other quality problems. For example, it did not consider nonconforming product as part of the regular analysis of quality data sources.

Acumedia also failed to investigate the cause of nonconformities related to the firm's product, processes, and quality system. For example, the company initiated a CAPA report after receiving a complaint that a particular product did not have labels. However, it failed to conduct a root-cause investigation or take any other action, the FDA found.

In addition, Acumedia was cited for failing to identify the actions needed to correct and prevent the recurrence of quality issues. For example, it opened a CAPA report to address a failure to adequately establish procedures for monitoring and controlling a validated process. This report was determined to be effective and was closed on June 29, 2016. However, a review and a recommendation related to retrospective validation were never completed.

The company also issued correction letters to customers describing nonconforming products but did not notify the FDA. Moreover, its product recall procedures did not include a provision to document a justification for not reporting a correction or removal action.

Inspectors also reported that the firm did not establish adequate procedures for monitoring and controlling process parameters, ensure that equipment maintained an acceptable temperature range, or provide adequate resources to ensure that the quality control system met regulatory requirements.

Read the Form 483 here: www.fdanews.com/01-06-17-Acumedia.pdf.

Becton Dickinson Caribe Gets Form 483 for Poor Procedures

Becton Dickinson Caribe received a Form 483 for its corrective and preventive action (CAPA), device acceptance, and process validation procedures.

The FDA inspected Becton's Juncos, Puerto Rico, facility and reported that CAPA procedures were not adequately established. CAPA actions implemented in response to confirmed product failures and for which root causes had been attributed to the manufacturing process did not extend to all impacted products, including products distributed before the corrective actions were implemented.

For example, a situation analysis was initiated as a result of an increased frequency of complaints regarding blood leakage, blood splatter, inadequate tube filling, and other problems with the BD Vacutainer Blood Transfer Devices. Device samples subsequently failed the acceptance criteria for leak testing, but no corrective actions were implemented for some affected products.

Inspectors also said Becton failed to adequately establish device acceptance procedures. In particular, test methods used to challenge for required product specifications were not properly validated, and acceptance activities to challenge for device specifications were not able to measure for the required range of products specifications.

Lastly, the Form 483 said Becton failed to prevent the release of products during the execution of process validation activities when changes to process parameters were being validated to prevent the recurrence of reported failures, or when a validation exercise did not comply with required acceptance criteria.

Read the Form 483 here: www.fdanews.com/01-06-17-Becton.pdf.

BRIEFS

Teleflex Receives Marketing Clearance For its Arrow VPS Rhythm Device

Wayne, Pennsylvania-based Teleflex has gained marketing clearance for its Arrow VPS Rhythm device with optional TipTracker technology.

The device assists in placement and confirmation of a catheter tip in the superior vena-cava-cavoatrial junction and can be used with a broad range of catheter types and brands.

When paired with the single-use TipTracker probe, the device provides real-time visual navigation.

Bayer Issues Recall for Medrad Intego PET Infusion System Administration Sets

Bayer has announced a recall for Medrad Intego PET infusion system source administration sets because of the possibility of injecting particulates into patients.

The device delivers medications from a chamber to a patient through a needle inserted into a vein during nuclear medicine procedures. The particulates may be formed when the tip of the needle pushes through the rubber top of the vial. If this occurs, the particulate matter could enter into the patient and cause serious adverse health consequences including infection, damage of tissue, and death.

The devices were distributed from Oct. 9, 2008 through Oct. 11, 2016.

FDA Grants Clearance to Roche's Anti-Mullerian Hormone Test Elecsys

The FDA cleared Roche's anti-mullerian hormone (AMH) assay Elecsys for use in the assessment of ovarian reserve, the reproductive potential based on the quality and quantity of egg cells in the ovaries.

The automated device measures the AMH levels in blood samples. The fertility test offers a more standardized method of measuring ovarian reserve compared to other options such as vaginal ultrasound.

Roche secured a CE mark to sell the device in all countries accepting the approval.

Globus Medical Earns CE Mark For Excelsius GPS in EU

Globus Medical received a CE mark for its robotic trajectory guidance and navigation system, the Excelsius GPS.

The system is designed to support minimally invasive and open orthopedic and neurosurgical procedures, including those related to the cervical spine, sacroilium, long bones and cranium. It integrates with instruments to guide the placement of implants.

Global Medical acquired the product's developer, Excelsius Surgical, in January 2014.

FDA Issues Clearance to ivWATCH For Continuous Monitor

The medical device manufacturer ivWatch garnered an FDA 510(k) clearance for the use of its ivWatch Model 400 in pediatric patients under the age of 18.

The continuous monitoring device for a patient's IV detects medication or fluid leaks outside the vein into surrounding tissue. The product uses a non-invasive sensor to collect near-infrared light and detect changes in the tissue. In February 2015, the FDA cleared the device for patients 18 years and older.

Orthofix Earns FDA Approval, CE Mark for Bone Growth Stimulators

Texas-based Orthofix received an FDA approval and CE mark for its CervicalStim and SpinalStim bone growth stimulators.

The Class III medical devices rely on low-level pulsed electromagnetic fields to stimulate spinal fusion and trigger the body's natural healing process. The devices are designed for use in post-operative care following lumbar and cervical fusion surgical procedures.

Abionic Secures CE Marks For Sepsis and Iron Deficiency Diagnostics

Abionic garnered CE marks for two diagnostic tests intended for the company's abioSCOPE device and designed for the assessment of sepsis risks and iron deficiency.

EC Plans to Lift Resale, Marketing Deadline for Non-Compliant Devices

The European Commission is planning to lift a July 22, 2019 deadline and allow certain second-hand and refurbished devices that contain hazardous substances to continue to be marketed in the EU beyond that date.

The EU's 2011 Directive on the Restriction on the Use of Certain Hazardous Substances (RoHS2) prohibits non-compliant electronic medical devices, IVDs, and industrial monitoring and control instruments that were already on the market before specified dates from being marketed after July 22, 2019.

The ban would greatly restrict the availability of second-hand and refurbished devices, according to attorney Cándido García Molyneux at Covington & Burling.

The RoHS2 Directive prohibits importation and marketing of electronic medical devices and other equipment that contain the hazardous chemicals. The ban took effect on July 22, 2014 for electronic medical devices and electronic monitoring and control instruments.

A similar ban on electronic IVDs took effect on July 22, 2016. A ban on electronic industrial monitoring and control instruments containing hazardous chemicals will take effect on July 22, 2017.

The Commission is expected to formally introduce the proposed amendment to the directive early this year. It will need approval by the European Parliament and the Council of the European Union.

FDA Pre-RFD Process Would Apply To Device-Drug Combo Products

The FDA issued a draft guidance on the preliminary request for designation process and what information to include. The pre-RFD process provides feedback on the regulatory identity or classification of a drug, biologic, or combination product, which could include a medical device.

The process has fewer requirements than the full RFD program, and can be helpful if a product is very early in its development, or if the product's classification — or the agency center it would be assigned to — is unclear or in dispute.

The guidance recommends paying special attention to the product description, why it would be used, and how it works — and in the case of combination products, the relative contribution of each component. In addition, the sponsor should include any marketing claims planned for the product, and whether the combination product will be marketed as a whole or by its constituent parts.

A pre-RFD application must include a listing of all components and ingredients, as well as instructions for the product's use.

Applications can be submitted to the FDA's Office of Combination Products, which will conduct a preliminary assessment for the application's completeness within five business days and alert the sponsor before beginning the full review.

If approved, the office will issue an initial classification, saying whether CBER, CDER or CDRH will regulate the product or hold primary jurisdiction.

The draft guidance is available here: www.fdanews.com/01-12-17-Pre-RFD.pdf.

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Mobile Medical Apps: *Keeping Up with the FDA's Evolving Requirements*

Just because an app is running on an unregulated phone or tablet doesn't mean that the app itself isn't a medical device in the FDA's eyes.

Where does the agency draw the line between unregulated products and those it must approve?

The final guidance for *Mobile Medical Applications* helps clarify the FDA's position on regulating mobile apps, but leaves several areas open to interpretation.

You need to know:

- How the FDA categorizes mobile apps and decides how — or whether — to regulate them as medical devices.
- How the FDA evaluates an app's "intended use."
- How to interpret the FDA's promise of "enforcement discretion" for certain types of apps.
- Who can be considered a mobile medical app developer and what regulations affect them.

This management report interprets the FDA's evolving stance on mobile apps and explains how the FDA sorts mobile apps into three categories:

1. **Administrative health information technology** (e.g, billing, claims processing, general communication and scheduling): This is not a medical device and not regulated by the agency.
2. **Health management information technology** (e.g., medication management, data capture, electronic access to clinical results, provider order entry): This is under FDA jurisdiction but generally so low risk that the agency can exercise enforcement discretion and not apply regulations.
3. **Medical device health information technology** (e.g., computer-aided detection and diagnosis, robotic surgical planning, remote display of bedside alarms, radiation treatment planning): This is actively regulated under Class I, Class II and Class III medical device rules.

Mobile Medical Apps explains what the FDA means by enforcement discretion and how it considers an app's intended use in category assignment.