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China Releases First-Ever Draft Guidance On Clinical Trials for Medical Devices

After releasing 186 new standards for medical devices last month, China FDA has now released details on how it will regulate clinical trials and on-site inspections for devices.

The agency outlines compliance policies and how it will authenticate clinical trial data, in its first-ever draft guidance on clinical trials for devices. The document also discusses which devices will be exempt from clinical studies.

"Previously, there were no legal documents regulating on-site inspections for medical device clinical trials," said Katherine Wang, partner at Ropes & Gray LLP. "These new drafts, for the first time, introduce a checklist and process for on-site inspections."

By increasing the frequency of on-site inspections, CFDA hopes to uncover fraudulent data more quickly and stop such practices by eliminating devicemakers without sound quality systems.

(See **China***, Page 2)*

MDIC Unveils Draft Blueprint For Early Feasibility Study Success

The Medical Device Innovation Consortium has developed a blueprint for U.S.-based early feasibility studies that provides an overview of best practices and ways to maximize positive outcomes.

Developed to supplement the FDA's Center for Devices and Radiological Health guidance on EFS, the blueprint covers industry interactions with the FDA and institutional review boards, legal and intellectual property considerations and patient perspectives.

Though the FDA issued guidance aimed at bolstering U.S. early feasability studies in 2013, an estimated 50 percent of MDIC members said their companies had not yet adopted those kinds of studies, according to a 2015 internal survey. While many members did reveal a desire to conduct U.S.-based EFS, they first wanted to see documented success with the program.

(See **MDIC***, Page 4)*

China, *from Page 1*

The guidance provides checklists via three annexes that outline specific duties for inspectors. The move adds consistency to the on-site inspection process and means that devicemakers can streamline their operations better.

Annex 1 documents requirements for clinical trials of medical devices and IVDs for the following categories:

- Clinical trial conditions and compliance;
- Informed consent;
- Clinical trial data management;
- Management of tests; and
- Reporting and registration of clinical trials.

Annex 2 creates a brief checklist for authenticity of clinical testing and trials.

Annex 3 details a clinical trial site inspection program from preparation for inspection to filing final reports.

In a follow-up document, CFDA proposes Class II and III medical devices that are exempt from clinical trials. The exemption applies only to products that follow established standards. If the product uses new materials, design or products, CFDA requests a clinical trial.

The Class II document lists 250 types of lower-risk devices without noting modifications that would require a clinical trial. The Class III document covers 93 types of devices with defining characteristics of exempt products along with examples of modifications that would require a clinical trial.

"Companies intending to launch new devices in China are advised to review their current practices, upgrade their compliance standards to the extent necessary and strictly comply with the upgraded standards," Wang advises.

But resource constraints will force the agency to conduct random inspections rather than hit all devicemakers. Wang said CFDA would conduct sample inspections "based on complaints regarding the authenticity, compliance and integrity of clinical trial data."

In May, CFDA set forth 186 standards devices need to meet, as well as parameters for testing, rules of inspections and other technical requirements (*IDDM*, May 13). — Joya Patel

ANSM Inspections Reveal Validation, Qualification Shortcomings

Inspections conducted by France's ANSM of makers of implantable defibrillation leads found qualification and validation processes were the largest compliance problems.

Between November 2013 and June 2014 the agency conducted audits at six sites for St. Jude Medical, Medtronic, Boston Scientific and Sorin. German manufacturer Biotronik refused to be inspected.

Findings revealed manufacturers generally met EC marking requirements.

The areas identified for improvement were:

- Qualification plans for each site and sterilization chamber;
- Validation of ethylene oxide re-sterilization on the device performance and the packaging strength;
- Validation of sterilization processes; and
- Qualification of controlled atmosphere areas.

In terms of risk analysis, major deviations encountered were:

- Lack of complete risk analysis plans;
- Inefficient approaches to risk-benefit analysis and residual risk;
- Batch release management by the production unit; and
- Lack of qualified management staff with documented assigned responsibilities.

The agency noted that an injunction was issued to one devicemaker for two of its sites in Minnesota and Puerto Rico for failure to demonstrate biocompatibility of products and gaps in validation processes.

Read the inspection report here: www.fdanews.com/05-26-16-ANSMInspectionReport.pdf.
— Joya Patel

Expert: Complaint Handling, Risk Management Add Color to ISO 13485

Members of the medtech industry concerned that EU device regulations expected this summer will conflict with aspects of the new version of ISO 13485 can rest easy, one expert says.

Kim Trautman, executive vice president at NSF Health Services, reassured devicemakers during a recent FDAnews webinar that there should be no conflicts between the two, pointing out that European regulators helped in the revision process for the standard.

The new revision of ISO 13485 outlines the requirements for a comprehensive quality management system for the design and manufacture of medical devices and in vitro diagnostics and related processes and services.

Toward Global Harmonization

According to Trautman, the revision — unveiled in March — was intended to harmonize medical device regulatory activities worldwide, particularly as South American and Asian bodies are updating their quality standards.

For example, African nations have recently become actively involved in regulating medical devices, says Trautman. South Africa proposed medical device legislation two years ago, and Tanzania and other countries have formed the Pan-African Harmonization Working Party on Medical Devices and Diagnostics.

The latest version of the standard provides clarity on complaint handling — adding requirements that align with existing regulations — as well as risk management activities. In terms of the latter, Trautman advises industry to pay attention to the changes, adding "many manufacturers may have a bit of work to do … coming up to the level of risk management that's now required."

In addition, the 2016 version devotes an entire section specifically on design transfer, which refers to the process by which device design is translated to production.

Control of purchased product is also much more prominent in the new iteration, which references both external and internal suppliers.

One important item to note that while there is a three-year transition for 13485 2016, devicemakers shouldn't rest on their laurels. After March 1, 2018, only certificates for 13485 2016 will be issued, so devicemakers should know what their certificate deadline or end date is and "what that means to switching to the new version," Trautman said.

Further, all certifications to 13485 2003, or the EN2012 version, will become obsolete as of June 1, 2019.

Avoid Complacency

Trautman advises companies to obtain a copy of the revised standard as soon as possible.

"If somebody is telling you that the new version of the standard is not that different … they're [probably] not very familiar with the new standard because there [are] quite a bit of subtle nuances that might not be obvious to a casual reader," she said.

To understand the nuances of the revision, she recommends that staff members pore over the standard and compare it to the older version as "a lot of things could be easily overlooked."

As companies transition, they should consider the resources they will need and conduct a gap analysis to assess areas requiring an overhaul.

She noted that the new version brings some aspects closer to 21 CFR 820, such as process validation and complaint handling. She noted that the software validation for quality management software addition closes the gap even further.

Trautman says that technical report 14969, which provides guidance on the application of ISO 13485, will not be updated. Instead, the body will provide a relatively new guidance mechanism in the form of a handbook to help manufacturers. It is in draft form, with final publication expected by the end of the year.

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Respondents reported that regulatory processes in the U.S. presented significant challenges for EFS. Moreover, the majority of respondents said they have conducted or plan to conduct their EFS overseas to avoid regulatory red tape.

"These challenges remain significant and need to be addressed in order to promote EFS in the United States," the MDIC report said. The organization said the survey identified a lack of information and an opportunity to provide more education and training for stakeholders interested in conducting an EFS in the U.S.

Early feasibility studies are used to provide proof of concept and initial clinical feasibility and safety data. They are generally carried out on a limited number of patients at a small number of investigational sites, and are an important tool early in the development process when additional nonclinical testing methods are no longer sufficient.

The report clarifies that the goal of an early feasability study "is not to prove the device performs exactly as intended and requires no changes, but rather to provide information to help you make a better, more effective device." It also notes that EFS are not always needed because often risks are mitigated by prior evidence that the design of the device is final or near final.

However, there are potential benefits to early feasabillity studies for patients, including earlier access to the device. This is especially beneficial when there are limited therapeutic options.

Another potential benefit for devicemakers is earlier regulatory input as well as input from technical experts and key opinion leaders.

In addition, good and credible EFS data is especially important for sponsors and smaller companies that need access to funding, the blueprint says. This is because positive EFS data can allow for: assurance of patient protection; an appropriate patient population and standard of care to support pooling of results later; good clinical practices; and a shorter time to market.

Since EFS require constant communication among mutiple stakeholders and organizations, the blueprint highly recommends that companies develop a comprehensive execution plan before they get started. To that end, the document suggests sponsors have in place a strategic device evaluation roadmap with objectives, milestones and timelines clearly defined.

The next step for MDIC's early feasibility working group is to incorporate comments into a finalized blueprint to be released this summer. MDIC has already received useful comments aimed at improving the informed consent template, a spokeswoman told *IDDM*. The final blueprint will also include a more thorough section on reimbursements.

To view the MDIC draft blueprint and leave a comment, visit www.fdanews.com/05-27-16-MDIC.pdf. — Jason Scott

FDA Approves First Blood Test to Detect Non-small Cell Lung Cancer

The FDA approved its first blood-based genetic test to detect epidermal growth factor receptor gene mutations in non-small cell lung cancer patients.

The Cobas EGFR Mutation Test v2, manufactured by Roche Molecular Systems, is a blood-based companion diagnostic for the cancer drug Tarceva. The diagnostic detects EGFR gene mutations, present in 10-20 percent of NSCLC patients.

NSCLC tumors shed tumor DNA into a patient's blood, making it possible to detect specific mutations in a liquid biopsy with minimal invasiveness.

Tarceva, manufactured by Astellas Pharma Technologies, was approved by the FDA in 2004 to treat patients with metastatic NSCLC after failure of at least one prior chemotherapy regimen. In 2013, the FDA approved it for treatment of patients with metastatic non-small cell lung cancer whose tumors having EGFR mutations as detected by an FDA-approved test. — Joya Patel

FDA Updates IDE Categories For CMS Coverage Decisions

The FDA is changing the way it categorizes investigational devices in an effort to help the Centers for Medicare & Medicaid Services make coverage determinations.

The FDA lays out the framework CDRH and CBER intend to follow when categorizing investigational products based on risk in June 1 draft guidance.

The document follows a memorandum of understanding executed last December by CDRH and CMS's Coverage and Analysis Group intended to aid reimbursement decisions for investigational devices. The MOU took effect June 2.

Two-Decade Facelift

The draft document updates policies that have been in place for two decades. In 1995, CMS, then known as the Health Care Financing Administration, and the FDA unveiled an agreement through which devices with an FDA-approved IDE could be covered by Medicare.

At the time, the FDA agreed to assign investigational devices to one of two categories, based on potential risks: Experimental/investigational (Category A) or non-experimental/investigational (Category B). There were a combined total eight subcategories in both groups.

Category A products were generally Class III, or device types whose safety and effectiveness had not been determined.

Those in Category B typically were Class I or II or Class III device types whose safety and effectiveness profiles were established.

Under Category A, coverage is allowed for routine care items and services furnished in the study, but not of the device itself. In a Category B IDE study, coverage is allowed for the device and the routine care items and services in the trial.

Although this system has worked for two decades, the FDA acknowledges it has received more IDEs that do not fit in these subcategories.

As a result, the FDA plans to assign investigational devices to Category A if at least one of the following criteria is met:

- No PMA approval, 510(k) clearance or de novo request has been granted for the proposed device or similar devices, and non-clinical and/or clinical data on the proposed device do not resolve initial questions of safety and effectiveness;
- The product has different characteristics than a legally marketed device; and information related to the marketed device does not resolve initial questions of safety; or
- The device is being studied for a new indication or intended use.

Products assigned to Category B will meet one or more of the following criteria:

- No PMA approval, 510(k) clearance or de novo request has been granted; however, available clinical data and/or non-clinical data for the proposed device or a similar device resolve the initial 308 questions of safety and effectiveness;
- The proposed device has similar characteristics compared to a legally marketed device, resolving the initial questions of safety and effectiveness; or
- The proposed device is being studied for a new indication or new intended use, and information from the proposed or similar device resolves the initial questions of safety and effectiveness.

The document provides examples of when Category A or B determinations may be appropriate, as well as instances when a device could change from Category A to B.

There are situations in which further data could resolve initial questions of safety and effectiveness and justify a change in device category. For example, when a completed study results in data that resolve initial questions of safety and effectiveness, the device could be reclassified as Category B.

Interested parties may comment through Aug. 1. Read the guidance document here: www.fdanews.com/06-06-16-guidance.pdf.

FDA Hits C-PAP Maker Somnowell with Warning Letter

C-PAP devicemaker Somnowell landed a May 12 warning letter for numerous quality system violations, including failure to establish procedures for quality audits and management reviews.

The specification developer located in Bellevue, Tennessee was inspected Feb. 11 through March 10.

According to the letter, the firm failed to establish procedures for conducting quality audits, management reviews or procedures for evaluating suppliers. Indeed, the firm had not conducted any quality audits, supplier audits or management reviews.

Inspectors noted the firm did not establish a design history file to demonstrate that its C-PAP device was developed according to the approved design plan. Similarly, procedures were not established for design changes or for implementing corrective and preventive actions.

The firm also did not maintain a complaint file and had not established procedures for handling complaints, the agency said.

Read the warning letter here: www.fdanews.com/06-02-16-SomnowellWarningLetter.pdf. — Joya Patel

Australia Issues Hazard Alert on Zimmer Biomet Knee Implants

Australia's TGA is cautioning healthcare providers that Zimmer's Trabecular metal knee implant may contain non-sterile implant components that could result in post-operative infection.

Zimmer's implants are packaged in a dual-barrier pouch containing an inner and outer pouch designed to provide sterile integrity. Testing conducted by Zimmer Biomet found tears in specific lots of foil packaging containing implant components in either inner or outer foil.

Potentially affected implants were distributed between April 2011 and March 2016. Clinicians are asked to inspect packaging and not use implants if any damage is visible. — Joya Patel

FDA Reclassifies Ophthalmic Device

The FDA is reclassifying the diurnal pattern recorder system from Class III into Class II to mitigate ocular risks.

Effective May 31, any firm submitting a premarket notification for a diurnal pattern recorder system will need to comply with the special controls prior to marketing the device.

A diurnal pattern recorder system is a nonimplantable device incorporating a telemetric sensor that detects changes in ocular pressure.

For this type of device, FDA has determined that premarket notification is necessary to provide reasonable assurance of the safety and effectiveness of the device.

Read the final order here: www.fdanews.com/06-02-16-DiurnalRecorderSystemClassification.pdf. — Joya Patel

FDA Beefs Up Expanded Access for Medical Devices

The FDA provided new clarity on the requirements for gaining access to investigational devices and the application process to gain access.

Patients and physicians have the potential to gain expanded access under one of three alternative mechanisms: emergency use, compassionate use and treatment use.

If necessary criteria are met, an unapproved device may be used in an emergency situation without prior approval by the FDA. Included in the new information is a physician's list of patient protection procedures that must be obtained to demonstrate benefit, including authorization from the device manufacturer. The sponsor must report emergency use of an IDE to the FDA within five days.

The compassionate use section has been expanded to cover devices that are being studied in a clinical trial under an IDE for patients who do not meet inclusion requirements under the clinical trial protocol. Compassionate use can also be gained for devices that are not being studied in a clinical trial or when an IDE for the device does not exist.

The FDA outlines how to request a compassionate use approval, and clarifies that a manufacturer must agree to provide the investigational device for compassionate use. If the device manufacturer agrees, there are two different tracks to proceed, depending on whether or not there is an IDE for a device.

The notice reports a roughly 99% approval rate for compassionate use requests, stating requests with IDE's were reviewed on average in 18 days and those without IDE's an average 10 days.

After compassionate use is awarded, companies must submit a follow-up report to the FDA with data on patient outcomes. Any problems need to be reported to the institutional review board immediately.

Read the FDA's updated Expanded Access for Medical Devices here: www.fdanews.com/06-02-16-ExpandedAccessforMedicalDevices.pdf. — Joya Patel

FDA Grants EUA to Idylla Ebola Virus Triage Test

The FDA granted an emergency use authorization for an Ebola diagnostic test developed in partnership by Janssen, Biocartis and the Belgium Institute of Tropical Medicine.

The Idylla Ebola Virus Triage Test detects Ebola RNA in venous whole blood in roughly 100 minutes.

The triage test builds upon prior diagnostics, streamlining the process by using a standardized automated system that requires minimal training for interpreting results.

The triage test differs from its counterparts in that blood samples collected in the sealed cartridge need no further manipulation, and the test does not require cold storage.

The EUA can be found here: www.fdanews.com/06-02-16-IdyllaEUA.pdf. — Joya Patel

BRIEFS

FDA Warns on Sorin Heater-Cooler System

The FDA updated health-care providers that Sorin's 3T Heater-Cooler System could be contaminated with M. chimaera if purchased before September 2014.

The agency warns that there may be a higher risk of infection associated with surgeries that introduced a prosthetic product or material when the 3T device was used.

Sorin issued Class II recalls for the device in July 2015 and March 2016.

In December 2015, the FDA issued a warning letter to Sorin Group Deutschland GmbH for its 3T Heater-Cooler System after inspections conducted at facilities in Munchen, Germany and Arvada, Colorado revealed significant issues, including quality system and premarket clearance violations (*IDDM*, Jan. 11).

The FDA's Circulatory System Devices Panel of the Medical Devices Advisory Committee is scheduled to meet in early June to discuss recommendations for sampling, notification, patient follow-up and monitoring of the 3T and other heater-cooler devices.

Read the FDA Safety Communication here: www.fdanews.com/06-02-16-Sorin3THeaterCoolerSafetyCommunication.pdf.

FDA Classifies Hummi Recall as Class I

Hummingbird's recall of Hummi Micro-Draw Blood Transfer device has been classified as Class I due to risks associated with potential disconnection, which can lead to blood or fluid leakage.

Hummi Micro-Draw is used to collect blood samples from infants, including premature infants. Serious adverse effects are associated with blood or fluid loss, including death.

The blood transfer systems were manufactured from June 29, 2015, to Dec. 2, 2015, and distributed from Oct. 26, 2015, to Nov. 18, 2015. A total of 37,750 units were distributed to California, Kentucky, Maryland and Illinois.

Hummingbird Med Devices has notified hospitals of this **recall** and recommended they not use blood transfer devices affected by the recall.

Imaging Agent Netspot Nabs FDA Approval

The FDA has approved Netspot, a radioactive diagnostic imaging agent for use in PET imaging.

The first kit for preparing gallium Ga 68 dotatate injection, Netspot is used to locate and assess tumors in adult and pediatric patients with somatostatin receptor positive neuroendocrine tumors (NETs).

Advanced Accelerator Applications plans to market the agent in the U.S. as soon as possible and will commercialize the product in two forms: as a kit for reconstitution using a Ga 68 generator and as a ready-to-use dose.

Granted priority review by the FDA, approval is based on results from three studies of the product, confirming the usefulness of Ga 68 dotatate images in finding the location of the neuroendocrine tumors.

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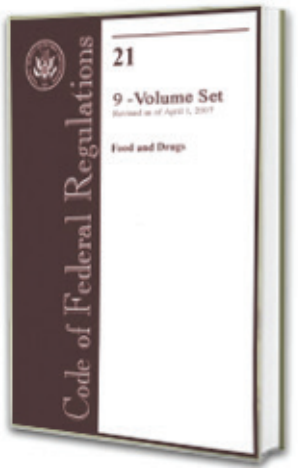

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