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IN THIS ISSUE

FDA Releases Guidances on Dual 510(k)–CLIA Waiver Submissions, Test Accuracy

The FDA issued two draft guidances to encourage using the 510(k)-Clinical Laboratory Improvement Amendments (CLIA) waiver dual application pathway for new in vitro diagnostic devices, and to update its policies for demonstrating accuracy to obtain a CLIA designation.

Under current regulations, clinical laboratories must obtain CLIA waiver certificates to perform tests that are "simple laboratory examinations and procedures that have an insignificant risk of an erroneous result," and these include those that "employ methodologies that are so simple and accurate" that a user's erroneous results can be rendered "negligible," the agency said.

The process industry historically followed was to obtain a clearance or approval of an IVD test designed for CLIA-waived settings, and to then apply for a CLIA certificate.

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China FDA Issues Guidance on Accepting Foreign Clinical Data for Medical Devices

China FDA will soon begin accepting foreign clinical data for medical devices as part of a national effort to promote industry innovation and to remove barriers to expediting reviews.

It recently released technical guidance that outlines requirements for those planning to submit foreign clinical data, and said the efforts will also help to avoid duplication for companies conducting global clinical trials.

The new guidance provides details on the clinical trial data needed to assess the safety and efficacy of medical devices and in vitro diagnostics intended for registration in China.

The guidance notes that clinical trials conducted abroad should conform to CFDA good clinical practices (GCP). If a trial is conducted in a country that does not have GCP requirements, the differences should be described in detail to demonstrate that they will not

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The optional dual submission pathway — created by MDUFA III in 2012 — is in "many instances the least burdensome and fastest approach" as it allows sponsors to simultaneously meet the requirements for both 510(k)s and CLIA designations, the FDA said, adding that it is especially appropriate for simple devices subject to premarket notification requirements with fail-safe and failure alert mechanisms, and requiring only a few pre-analytical steps.

The new draft guidance outlines recommendations on what to include in a dual submission, such as a device description that demonstrates simplicity, and on designing comparison and reproducibility studies in support of the submission. An industry commitment, established earlier this year as part of MDUFA IV, requires applicants to inform the FDA of their intent for a dual submission.

But the expectation is for the use of this pathway to reduce the FDA's overall review time for the submissions. For IVD manufacturers, the agency hopes the guidance will also help reduce study-related costs and save them time during the submission process.

"FDA believes increased use of this pathway will speed up the process of bringing simple and accurate IVD devices to CLIA-waived settings, which will better serve patients and providers," the agency said.

Accuracy is a key element for granting a CLIA waiver, according to the FDA. In a separate draft guidance document, the agency proposed to revise its CLIA Waiver Guidance from Jan. 30, 2008, as required by the 21st Century Cures Act of 2016.

The FDA said that, when finalized, changes to the 2008 guidance will provide "additional details and pathways for demonstrating that a test has an insignificant risk of erroneous result[s]."

Read the Recommendations for Dual 510(k) and CLIA Waiver by Application Studies draft guidance here: www.fdanews.com/11-30-17-510kCLIAWaiver.pdf.

Read the Select Updates for Recommendations for CLIA Waiver Applications for Manufacturers In Vitro Diagnostic Devices draft guidance here: www.fdanews.com/11-30-17-CLIAWaiver.pdf.

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have an effect on the authenticity, scientific rigor, and reproducibility of research results, and that human research subjects will be protected.

Applicants should include a clinical trial plan and ethics committee opinion. They should confirm that the population data studied can be extrapolated to the Chinese population, and they should contact China's Center of Medical Device Review before submitting the data from clinical trials conducted in foreign countries.

These moves are expected to create a level playing field for R&D-focused device companies at home and abroad, according to the law firm Ropes & Gray in Shanghai.

Launches of imported devices have historically lagged behind first device launches in their country of origin because the CFDA required advance approval on a phase-by-phase basis before clinical trials could begin.

Further, the "shortage of CFDA-qualified clinical study sites limits the infrastructure for clinical development, and increases study costs," the attorneys said.

CFDA also intends to enhance the clinical trial approval process. It will allow devicemakers to begin clinical trial studies following a 60-day waiting period if the CMDE does not object to their application filing or issue a deficiency notice.

Devices that offer new solutions for treating life-threatening diseases or address critical unmet medical needs could be eligible for conditional approvals, as long as early and mid-stage study data indicate efficacy and clinical value. Those approved outside of China that offer new solutions for treating rare diseases will also be eligible for conditional approvals.

China recently tightened up on its policing of clinical trials, with the Supreme People's Court requiring stricter punishments for companies falsifying clinical trial reports (*IDDM*, Oct. 16).

Health Canada to Revise Guidance On Investigational Device Testing

Health Canada is revising its guidance issued in 1999 on investigational testing authorizations for medical devices.

The guidance is intended to aid device manufacturers and importers in the submission process for ITA applications to conduct investigational testing of a Class II, III or IV device, and provide details on their responsibilities when testing Class I devices.

The previously released guidance is "no longer adequate and lacks clear and consistent guidance on a number of aspects regarding the preparation of applications for ITAs," Health Canada said in a new draft guidance, which was prompted by frequent requests for clarification from device manufacturers.

Health Canada intends to only issue an ITA after receiving evidence of approval from a research ethics board (REB) for Class III and Class IV devices, and the authorization will be valid until the device is licensed as long as the REB approval is current.

For Class I devices, obtaining ITAs is not a requirement for a manufacturer or importer to sell a device to an investigator for investigational testing, though these must also receive REB approvals, as well as meet institutional requirements.

The guidance covers the use of recognized standards, drug-device combination products, investigator-sponsored investigational testing, stages of product development, revisions to an investigational testing protocol, and problem reporting. It does not cover in vitro diagnostics.

If several devices are to be included in an investigational study, separate ITA submissions are required for each device. The guidance also includes detailed examples of the required content for ITA submissions.

Health Canada is encouraging manufacturers and importers to request a pre-ITA application meeting, particularly for novel Class III and Class IV devices and combination products.

The meetings may provide a manufacturer or importer an opportunity to present data relevant to an ITA application and discuss any concerns or issues regarding product development. For the regulator, these meetings may also present opportunities to provide guidance and highlight potential deficiencies or concerns.

Interested parties should submit requests for meetings to the Investigational Testing Division of the Medical Devices Bureau. These should include a synopsis of the proposed study and a list of preliminary questions to be addressed during the meeting. Sponsors should include sufficient information so the regulatory authority can assess the utility of the meeting and identify appropriate staff to attend.

Read the draft guidance here: www.fdanews.com/11-28-17-Canada.pdf.

FDA Finalizes Guidance to Limit Radiation Exposure With X-Ray Imaging

The FDA released final recommendations for manufacturers of x-ray imaging devices aimed at clarifying the premarket review process and encouraging pediatric indications.

The recommendations, drafted in 2012, outline how the devices can be designed, tested, and labeled with the goal of helping medical professionals make more informed decisions on radiation doses during x-ray imaging exams to limit unnecessary exposure.

Exposure to ionizing radiations is particularly concerning with younger patients as they are more radiosensitive than adults, the likelihood of the effects manifesting as cancer is greater, and exposure settings intended for adult use can result in children being overexposed, the FDA said.

The risk of developing cancer from excessive radiation exposure is slight but "it is real and compels us to be proactive about reducing patients' exposure as much as possible, without jeopardizing the diagnostic quality of the exam," Vasum Peiris, CDRH's chief medical officer for pediatrics and special populations, said in an FDA Voice blog post.

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Gottlieb Previews Upcoming Guidances on Complex Generics

The FDA is working to develop and finalize a handful of new guidances on bringing complex generics to market — including drug-device combination products that may be blocked by iterative patents.

At the agency's Generic Drug Science Day, Commissioner Scott Gottlieb offered a small preview of the upcoming documents and policies, but did not offer details on when they would be published.

The FDA is currently finalizing a draft guidance that urges sponsors to minimize device design changes in generic drug delivery products, and outlines how differences could threaten substitutability.

However, the final version will clarify new agency policies that will allow certain labeling differences stemming from permitted changes in the generic product's design, Gottlieb said.

As long as the generic sponsor can demonstrate the differences do not affect the clinical benefit or safety profiles when substituted, the generic product can be approved as a competitor.

The FDA is also working on internal policies that may delay approval of generic drug-device combinations. Gottlieb noted how a lot of open complex drugs may still lack competition, even without the obstacle of patent or exclusivity protections.

"In many of these cases, it's because the scientific principles for proving sameness have not been firmly established," he said, adding that the agency is currently developing a guidance to clarify sameness requirements for ANDAs.

Delivery devices, such as metered-dose inhalers or auto-injectors, can also cause complications and be difficult to copy. — Conor Hale

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The FDA recommended that manufacturers, as part of their device design, perform a risk assessment that considers specific risks and mitigations arising from the use of their device in pediatric populations to minimize the risk of excessive radiation exposure.

In terms of labeling, it is recommended that the pediatric summary includes this caution statement: "Use special care when imaging patients outside the typical adult size range." The devices should also be designed to be easy-to-use with clear instructions on optimizing doses.

The guidance applies to existing x-ray imaging devices as well as new ones, though it is meant to be used with device-specific guidances and the general policies for 510(k) submissions. If user-requested modifications are made on existing devices to optimize imaging parameters and pediatric-specific protocols, new 510(k) submissions will not be required, the agency said.

"These recommendations, while significant and capable of making an important difference in the amount of radiation pediatric patients receive, also strike the right balance between safety and burden to manufacturers," Peiris said.

Read the Pediatric Information for X-ray Imaging Device Premarket Notifications guidance here: www.fdanews.com/11-30-17-Pediatricinfoxray.pdf.

MedTech Europe Calls for Building Blocks To Implement EU Regs On-Time

EU authorities must take swift action on three essential building blocks to implement the new regulations for medical devices and in vitro diagnostics smoothly and on-time, MedTech Europe said in three new position papers.

The trade association called on the European Commission to invest more resources, to ensure the capacity and availability of notified bodies, and to ensure a consistent interpretation of the transition periods – three years for medical devices and five for IVDs.

Ultimately, the goal is to prevent disruption to product availability during the transition periods, the industry group said. Last month, MedTech highlighted challenges with the Brexit plans that could impact product supply, and suggested ways to mitigate the risk of regulatory divergence (*IDDM*, Nov. 20).

Current resources in Europe are too limited to ensure the new regulatory regime will be successfully implemented within the desired timeframes, according to MedTech. More investment is needed in IT, for example, to address the expected resource challenges "in light of the substantial workload on the horizon," the association said. The notified body workload is expected to increase by about 780 percent for IVDs, with each notified body assessing an average of at least 1,600 IVDs.

Investment in staff is also needed to ensure there is a sufficient number of in-house staff with expertise in both regulations to assess the different kinds of candidate notified bodies, Oliver Bisazza, director for regulations and industrial policy at MedTech Europe, told FDAnews.

"The more staff authorities allocated to review and designate notified bodies, the more candidate NBs can have their applications reviewed in parallel," he said. "If there is a shortage of staff, some candidate notified bodies will inevitably be longer in queue, and their files will only be reviewed once the other candidate NBs at the front of the queue have been done."

He cautioned, however, that "authorities could double their staffing investments and it's all for nothing if those new staff work too slowly, or if they are not yet sufficiently trained."

Transition Periods

According to MedTech Europe, medical technology firms expressed concerns about a lack of clarity between authorities, NBs and industry on the transitional provisions and the implementation timelines for both regulations.

Transitional arrangements include designating notified bodies, harmonizing standards to the regulations, and setting up a new Eudamed database. These will take a considerable amount of time and most IVDs and MDs are not yet ready to comply, the group said.

Actions that may help address this issue include secondary legislation on how key provisions, such as those for the database, will work following implementation, and new governance and oversight for certifying certain high-risk devices.

Notified bodies

The industry is also concerned it will not be possible for the limited number of notified bodies to certify the "vast number of products early enough in the allotted transition period," according to MedTech, which represents more than 26,000 medical technology companies in Europe.

The association declined to specify how many notified bodies would be needed to address this issue. "The number is irrelevant at the end of the day," Bisazza said. What matters is "that there is sufficient NB audit/assessment capacity for all the many different types of IVDs and medical devices out there."

"If half of all existing NBs disappear, it might not matter in the long run, provided the remaining half 'absorbs' their capacity and expertise," he said.

(See **MedTech***, Page 6)*

Maquet Files Suit Against Abiomed Over Intravascular Blood Pumps

Maquet Cardiovascular filed a patent infringement lawsuit with the U.S. District Court for Massachusetts against Abiomed over the company's intravascular blood pumps.

Abiomed allegedly became aware of Maquet's patent No. 9,789,238 for its implantable devices that may be used to "supplement and even fully support" a patient's blood circulation around Aug. 24, 2016.

But Abiomed continued to directly infringe patent claims 1, 13 and/or 19 in manufacturing and selling its Impella 2.5, 5.0 and CP intravascular blood pumps, Maquet claimed.

The lawsuit seeks judgement against Abiomed for basic, induced, contributory and willful infringement, among other relief actions.

FDA to Exempt Surgical Apparel From 510(k) Requirements

Single-use, disposable respiratory protective devices used in healthcare settings by medical professionals may soon be exempt from premarket notification requirements.

The FDA is proposing to exempt the devices intended to protect patients and hospital staff from the transfer of microorganisms, body fluids, and particulate material, subject to certain limitations. They are currently regulated as class II (special controls) devices.

The 21st Century Cures Act gave the agency authority to exempt class II devices from requiring 510(k) submissions if it can determine that a 510(k) clearance is not necessary to assure their safety and effectiveness.

The agency entered into a Memorandum of Understanding with the CDC's National Institute for Occupational Safety and Health that sets out how the agencies will collaboratively regulate RPDs being proposed for exemption.

The MOU outlines the following conditions that respiratory protective devices, otherwise known as N95 filtering face piece respirators and surgical N95 respirators, must meet to qualify for exemption:

- The application submitted to NIOSH is determined not to exceed the CDC and FDA mutually agreed threshold evaluation criteria; and
- Applicants must have NIOSH approval.

All other class II devices classified under the FDA's surgical apparel classification regulation would continue to be subject to premarket notification requirements, the agency said.

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"In reverse, you could double the number of existing NBs and it also wouldn't solve the issue, for instance, if all new NBs were only competent to review one specific category of IVD or medical device."

Further, the regulatory framework for IVDs should be given as much of a priority as the framework for medical devices, regardless of their later transition, because the new regulations will expand the scope to more IVDs and these devices will also have to meet additional requirements, the association said. — Ana Mulero

483 Roundup: Devicemakers Cited For MDRs, CAPAs, Complaints, DHRs

The FDA flagged four firms for a range of violations including a failure to submit medical device reports to the agency for fatal adverse events.

SynCardia Systems: Tucson, Az.-based SynCardia Systems drew an FDA Form 483 for failing to submit MDRs on adverse event reports for about 70 deaths linked to the use of its device intended to help patients recover after undergoing surgery for artificial heart implants.

A four-day August inspection at the device manufacturing facility revealed it had received information between April 2014 and March 2017 about the deaths of patients who used its Companion 2 Driver System, but it did not submit any MDRs to the agency.

The firm was also cited for having inadequate procedures for device design changes. An FDA investigator reviewed the design history files for its Companion 2 Driver and its Freedom Driver System, and observed that pre and post PMA design changes were "neither included nor referenced in the documents."

Cadwell Industries: The FDA observed nonconformities related to CAPAs, complaint handling and design validation at Cadwell Industries' manufacturing facility in Kennewick, Wa.

The facility had no documented plan for verifying the effectiveness, as required by the firm's CAPA procedure, of at least two CAPAs that had already been marked as effective, according to the Form 483 issued after an August inspection.

The agency's investigator also found three complaints regarding devices that were returned to Cadwell more than a year ago that had not been evaluated. In addition, the firm had failed to follow its validation procedure for the IOMAX device as production equivalent devices were not used for testing.

BZ Medical: Written MDR procedures had yet to be developed at BZ Medical when the FDA conducted an August inspection at the medical device specifications developer's facility in Portland, Or.

The firm's complaint procedure was found to be inadequate in that it lacked provisions for conducting a standardized review of complaints to determine whether an MDR was required and for timely MDR submissions to the FDA, as well as documentation and recordkeeping requirements, the agency's investigator observed in a Form 483.

Other identified nonconformities relate to the firm's product purchasing procedures — deemed inadequate as its subcontractors had not been evaluated since 2015 or at all — internal quality audits not being conducted since 2012, and its procedures for device history records, which did not include a requirement for documenting labeling.

CME America: Out of 11 device history records at CME America's facility in Golden, Co., seven lacked documentation that should have identified existing nonconformities, an FDA inspection revealed.

The agency issued a Form 483 following the inspection conducted from mid-July to early August noting the firm's procedures for controlling the nonconforming products were inadequate.

CME America had also failed to include revisions made to its manufacturing operations in its device master record for the BodyGuard 323 Infusion Pump, and to provide documentation as evidence that validation activities had been conducted on its molding machines.

In a repeat observation, the agency cited the firm's procedure for evaluating potential suppliers.

Read the SynCardia Systems Form 483 here: www.fdanews.com/11-30-17-syncardiasystemsllc483.pdf.

Read the Cadwell Industries Form 483 here: www.fdanews.com/11-30-17-cadwellindustriesinc483.pdf.

Read the BZ Medical Form 483 here: www.fdanews.com/11-30-17-bzmedicalinc483.pdf.

Read the CME America Form 483 here: www.fdanews.com/11-30-17-cmeamericallc483.pdf.

APPROVALS

Medtronic Earns FDA Approval For Remote Patient Monitoring Pacemakers

Medtronic received FDA approval for its Azure pacemaker portfolio, which includes the Azure XT MRI and Azure S MRI.

The pacemakers allow for automatic, wireless remote monitoring, using Medtronic's BlueSync technology, for a care provider's evaluation of the patient's time sheets.

BlueSync includes security controls such as access restrictions to ensure device integrity and end-to-end encryption to protect patients' health data.

Implanted Lens for Post-Surgery Adjustment Snags FDA Approval

RxSight received the FDA's approval for the first medical device system that allows for artificial lens adjustments post-cataract surgery with UV light-reacting material.

The system consists of the firm's light adjustable lens and light delivery device. It was designed to eliminate the need for glasses, contact lenses or an additional surgery to address blurred vision after cataract surgery performed to replace an astigmatic patient's natural lenses with an artificial lens. The system allows the physician to make small adjustments to the implanted lens during in-office procedures after the initial surgery.

Hologic Wins FDA Clearance For Breast Density Software

The FDA cleared Hologic's Quantra 2.2 breast density assessment software for marketing.

The Quantra software uses an algorithm that can provide four categories of density assessments to clinicians performing routine breast cancer screenings. The device helps clinicians detect breast cancer in women with very dense breasts — who are up to five times more likely to develop the disease.

FDA Clears Medicrea's 3D-Printed Titanium Interbody Devices

Medicrea won FDA clearance for its 3D-printed titanium interbody devices for spine surgery.

The firm's IB3D suite allows surgeons to design patient-specific interbody devices. The custom implants are then created by the firm using 3-D printing additive manufacturing capabilities.

Biocartis Colorectal Cancer Assays Score CE Marks

Biocartis' two liquid biopsy tests for the detection of tumor DNA mutations in patients with metastatic colorectal cancer have received CE-IVD marking.

The Idylla ctNRAS-BRAF mutation test can detect 18 NRAS and five BRAF mutations, with results in 110 minutes. The Idylla ctKRAS can detect 21 KRAS mutations with results in 130 minutes. The RAS tests, developed in collaboration with Merck KGaA, require less than a minute of hands-on time.

Butterfly Medical Earns CE Mark for Prostate Device

Tel Aviv, Isreal-based device manufacturer Butterfly Medical received a CE Mark for its novel device for non-surgical, office-based treatment of Benign Prostate Hyperplasia.

The device offers an alternative to first-line drug treatment or surgery, and the treatment can be performed in less than 10 minutes.

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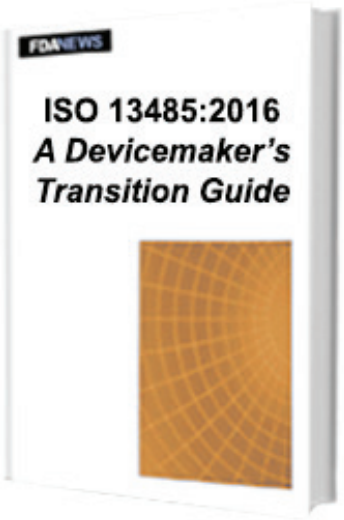

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