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Labs, Diagnostics Makers Gear up for FDA LDT Hearing; 83 Set to Speak

Clinical laboratory groups plan to mount a major push against the FDA's efforts to regulate lab-developed tests at a Jan. 8 and 9 public meeting, arguing that the FDA's plans will hinder LDT development and use.

Some groups even question whether the FDA has the statutory authority to regulate LDTs. "We have always maintained that we do not believe these are medical devices," says Alan Mertz, president of the American Clinical Laboratory Association. "These are laboratory services, used during the practice of medicine, and are not sold commercially."

And even if the FDA did have authority over LDTs, the ACLA believes the agency can't regulate them simply by issuing a guidance document, the approach the agency is taking, but only through formal rulemaking. Using the guidance process allows the FDA to avoid rulemaking provisions that require the agency to respond to each comment on a new rule, as well as conduct an economic analysis of how regulations will impact industry, Mertz says.

Labs Challenge Use of Guidance

Attorney and FDA regulatory expert Gail Javitt agreed the decision to proceed with guidance may not be legal. She noted that the regulations defining medical devices exempt clinical laboratories from FDA registration and listing requirements.

The proposed guidance advises LDT makers to voluntarily notify the FDA of LDTs being developed; it makes no reference to listing or registration. However, the notification standards would ask for more extensive information than is typically required in device registration and listing, such as updating the information every time the laboratory makes a significant change. She says the agency is disregarding longstanding principles of agency law and administrative procedure in the way it is proposing the new requirements.

But AdvaMedDx President Andy Fish says the FDA's authority to regulate LDTs is covered under longstanding diagnostics rules, so guidance is appropriate. The comment period on the guidance, which ends Feb. 2, and public meeting will allow adequate opportunities for all stakeholders to be heard, he says.

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AdvaMedDx firmly supports FDA regulation of LDTs because the tests are now increasingly sophisticated, are relying on molecular diagnostics, and are now being used to diagnose and choose treatment for critical life-threatening conditions even though there is no FDA or other third-party review for the tests. Further, he says, the FDA's plan to phase in the requirements over nine years and apply a risk-based approach to overseeing the LDTs provide laboratories with enough protection against being overwhelmed by new regulatory requirements.

The proposal has been controversial since it was announced this summer, with some touting FDA regulation as a win for patient safety while others see it as an FDA overreach that could be expensive for industry and destructive to patient access. A total of 83 representatives from manufacturers, trade groups, research organizations and patient advocacy organizations are scheduled to offer public comment during the meeting.

Revisions Rather Than Overhaul Urged

Roger Klein, chairman of the professional relations committee of the Association for Molecular Pathology, says his group proposes modernization of the Clinical Laboratory Improvement Acts instead of an FDA takeover of LDT regulation. He believes that several of the FDA's proposed changes would impose high costs on labs for little benefit.

For example, he says he has never seen death or a serious injury directly caused by the design of a lab test, and notes that CLIA already requires errors in testing results be reported to physicians. The costs of maintaining a formal adverse event reporting program would be substantial for a lab and offer no benefit. If adverse event reporting is imposed at all, he believes it should be limited to labs making FDA-cleared tests.

The ACLA's Mertz also expresses concerns over the costs, noting that diagnostics makers who obtain FDA approval often spend $10 million to $20 million on the process – more revenue than many LDTs ever generate, he says.

Several speakers say they plan to urge the proposal be modified in ways that would place labs and IVD manufacturers on equal footing. Sam Rua, vice president of regulatory affairs and quality systems at genomic testing start-up HTG Molecular Diagnostics, says he supports most of the guidance but finds parts of it overly restrictive. For example, the proposed guidance would say tests only qualify as LDTs if they are designed and manufactured entirely within a lab. "The FDA allows IVD manufacturers to use contract manufacturing," he says. "Labs should be allowed to do the same thing."

Sharing LDTs Should Be Allowed

The FDA's proposal to exempt tests used within a single research hospital from oversight also caused some concern. High-quality programs such as those at the Mayo Clinic or Cleveland Clinic sometimes share tests they have developed with smaller hospitals via outreach programs, Roger Klein of AMP says. But that informal sharing would seem to be banned under the FDA proposal.

Klein also questions a provision in the regulations that would define any lab that modified a cleared test as a re-manufacturer and subject to clearance requirements. "It's important to understand these types of modifications happen very regularly," he says, noting that sometimes tests are validated on one specimen type but may be modified to accept others as well. If labs had to notify the FDA every time they did this, labs would simply stop doing it. He wants the FDA to allow labs to use LDTs off-label, just as physicians may use drugs off-label.

Despite all the disagreement, HTG Molecular's Rua says he hopes the meeting allows industry and the FDA to find common ground. "Everybody understands that laboratories can get tests out much quicker than IVD manufacturers and that's in part due to the regulatory hurdles," he says. "I hope this will get more parity so the FDA is looking at the IVD community and labs under the same lens, with a similar least-burdensome approach."

The meeting is set to be webcast. View a speaker list and other information at www.fda.gov/MedicalDevices/NewsEvents/WorkshopsConferences/ucm423537.htm. — Elizabeth Orr

In 2014, the Focus Was on Regulatory Reform, Quality and Transparency

2014 was a year of major strides in streamlining regulatory processes around the globe. The International Medical Device Regulators Forum launched its single-audit pilot program, letting participating companies prove compliance in the U.S., Canada, Australia and Brazil based on one third-party assessment. China and Japan rolled out new regulatory frameworks aimed at speeding access to new devices, and Australia began accepting the CE mark for low- and medium-risk devices. In Europe, lawmakers and EU officials advanced proposals on medical device and in vitro diagnostics regulation, but couldn't reach agreement on a premarket scheme for the highest-risk devices, reuse of single-use devices and other key issues. Legislation to create a regulatory framework for devices also resurfaced in South Africa during 2014, while India took steps to improve device quality and impose international GMPs. Below, International Devices & Diagnostics Monitor *recaptures some of the main events of the year gone by.*

Regulatory Reform. EU lawmakers and members of the European Commission and Council of Ministers continued to debate the merits and shortcomings of proposed regulations on medical devices and in vitro diagnostic devices, with controversy centering around whether high-risk devices be subjected to intense premarket review — à la the U.S. Food and Drug Administration.

EU-Level Expert Panel Urged

Industry group Eucomed urged that the scrutiny of notified body procedure in the draft device regulation be replaced by a "reinforced control procedure" featuring more frequent and rigorous checks by Medical Device Co-ordination Group audit teams and the Commission of the Notified Bodies. To ensure the quality of conformity assessments, the group suggested a new EU-level expert panel be created to independently vet companies' clinical evidence as part of the review process.

As the new European Parliament got underway this past fall, following May elections, it was decided to move medical devices and IVDs from the health directorate to the Directorate for Industry and Trade. Industry largely welcomed the change, saying it put a greater focus on competition and the needs of small businesses.

Across the channel in the UK, the government announced a major review of how devices and diagnostics are developed, with the aim of speeding new products to market.

New Rules in China, Japan

On the other side of the world, a two-month transition time for five new regulations in China stoked concerns that supplies of products might be disrupted. The regulations, released in August, changed the way devices and in vitro diagnostics are registered in China, the rules on instructions for use and labels and supervision of device manufacturing and distribution. The regulations are part of a major regulatory overhaul that took effect June 1. Among other things, the risk-based reforms require that clinical trials be conducted in China for all Class II and III devices, unless they can show they are equivalent to a device already listed in the country.

In Japan, the Pharmaceutical and Medical Devices Agency launched a comprehensive regulatory framework for medical devices in late November, but devicemakers were still awaiting many of the implementing regulations as that deadline drew near, raising fears that products might be temporarily blocked from that market as well. The law, adopted in 2013, also creates a new category for cellular and tissue therapy products and calls for a provisional approval pathway to speed access to promising therapies. Separately, the PMDA eased its standards for use of biological raw ingredients in medtech products.

Elsewhere, Malaysia continued to implement its 2012 device regulations, issuing five notices on how to comply with the new law and a 12-step guideline on IVD registration submissions. The former included details on authorized representatives, conformity assessment procedures for

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products authorized by recognized countries and good manufacturing practice certification to support an establishment license.

In Australia, the Therapeutic Goods Administration announced it will now accept CE mark certifications issued by European notified bodies for low- and moderate-risk devices, relieving companies of the need for a TGA assessment. Meanwhile, Brazil's Anvisa issued draft resolutions that would ease registration of low- and medium-risk devices and diagnostics, and there were signs of renewed life in South Africa's long-overdue device regulations bill.

Inspections and Audits. The International Medical Device Regulators Forum successfully launched its Medical Device Single Audit Program with two audits in which the devicemakers were found to have only minor nonconformances. Participating companies were assured they wouldn't receive warning letters unless there was an imminent threat to the public health. Under the MDSAP pilot, slated to run through the end of 2016, an assessment performed by a single third-party auditor is sufficient to prove compliance in Australia, Brazil, Canada and the U.S.

Meanwhile in the U.S., the FDA announced a sweeping reorganization of its inspectorate that will include dedicated device investigators, eliminating the existing region-based model. Over time, investigators will be extensively trained in specific types of devices. CDRH has already identified one area that it intends to carve out as a subspecialty: radiological and mammography devices.

The specialized inspectorate is one piece of a larger plan to improve CDRH services, which includes creation of more metric-driven inspections and a five-year review of all compliance and policy guides.

And in the EU, notified bodies began conducting unannounced quality audits of companies that hold CE certificates for Class IIa and higher-risk devices. The surprise visits apply to all manufacturers that have products in the European

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Economic Area, regardless of where their manufacturing plants are located and come at a time when EU regulators and the U.S. FDA are moving toward sharing inspections data.

Halfway around the world, India took steps to improve device quality, proposing that manufacturers be required to follow international good manufacturing practices, while a private initiative took shape that will begin self-certifying companies' best practice.

Harmonization. During the year, IMDRF also finalized a risk-based framework for software as a medical device and documents on device and in vitro diagnostic submission tables of content. Meanwhile, the Asian Harmonization Working Party issued draft guidance on adverse event reporting timelines and a white paper on classifying and qualifying device software.

Also in the Pacific-Rim area, Australia and New Zealand abandoned plans to create a joint regulatory authority, but said they would continue to explore regulatory harmonization. New Zealand's health minister also promised to continue in-country regulatory reforms. Devicemakers in both jurisdictions welcomed the news, saying the potential benefits would not have offset the costs of setting up the new agency.

Also in Asia, South Korea's Ministry of Food and Drug Safety announced it was amending its electromagnetic safety standards for medical devices to align them with international standards.

Research and Development. During 2014, the FDA issued several guidance documents focused on improving device clinical trials. One, issued in March, explained best practices in designing studies for devices intended for use by pediatric patients. In August, the FDA published final guidance and an action plan on gender differences in clinical research. The agency wants sponsors to enroll patients in numbers proportionate to the disease prevalence and track those numbers throughout the trial.

South of the equator, the Brazilian government clarified criteria for participation in a program to expand access to affordable technologies through public-private R&D partnerships.

Transparency On Sept. 30, the U.S. government began publishing devicemaker payments to physicians, the latest provision of the Physician Payment Sunshine Act to take effect. Industry complained that the Open Payments Database lacks context, making it difficult for the public to gauge whether a payment was appropriate or not. The Centers for Medicare and Medicaid Services further riled industry by not including a reporting exemption for payments made to continuing medical education programs.

Across the pond, the European Parliament advanced major data privacy legislation, but not before removing a provision that would have allowed clinical research subjects to demand that personal data be erased from all records, even after they were incorporated in regulatory filings. Lawmakers also carved out exemptions to data usage rules to allow devicemakers to share anonymized trial data for research purposes.

Health IT. Concerns over safety and security of device software and medical apps remained high last year. A U.S. FDA report, mandated by the 2012 FDA Safety and Innovation Act, proposed a three-tiered, risk-based framework for categorizing software: products with administrative health IT functions; products with health management IT functions; and products with medical device health IT functions. The agency would closely regulate only the last category, which would include software that duplicates functions now performed by FDA-regulated devices. The proposal echoed legislative attempts to keep most types of software out of the FDA's purview, but still faced pushback from critics who believed it gave the agency too much discretion.

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On the security front, the FDA finalized guidance requiring manufacturers of medical software and apps to describe cybersecurity efforts in premarket submissions. Topics to address include hazard analysis, updates and maintenance throughout the device's lifecycle, and software integrity.

Laboratory-Developed Tests. The U.S. FDA signaled its intention to move forward on regulation LDTs with a July report to Congress and October guidance. The agency proposes classifying LDTs as low-, moderate- or high-risk within 18 months of issuing final guidance. Registration, listing and adverse event reporting requirements for Class II/III LDTs would take effect six months after the framework is finalized, with premarket requirements for Class III LDTs commencing six months later.

While supported by AdvaMed, the proposal faces notable opposition. The American Clinical Laboratory Association has asked the FDA to withdraw the draft and has retained attorneys for a possible court fight. Lawmakers have also asked the agency for clarification on how plans to regulate the tests.

Pricing and Reimbursement. Concerns about rising healthcare costs and patient access fueled technology assessments in the U.S. and EU. A voluntary network of European HTAs called for greater cooperation to avoid duplicating work related to device coverage decisions in individual EU countries, while the pan-European EUnetHTA proposed a framework to harmonize coverage decision guidelines in EU member states.

In the UK, the National Institute for Health and Care Excellence called for medtech cost-benefit assessments to include burden of illness. During the year, the watchdog agency also updated its guidance on cardiac devices and gave a positive nod to intrabeam radiotherapy for early breast cancer.

Meanwhile, India's National Pharmaceutical Pricing Authority set its sights on price controls for a group of notified medical devices regulated under the country's drug law. NPPA wrote to 10 manufacturers and importers in December demanding immediate pricing information, in response to media reports claiming that drug-eluting stents were being sold at exorbitant prices.

Device tax. In the U.S. the 2.3 percent medical device excise tax remained firmly in place, despite continued efforts by industry and some lawmakers to repeal it. The Internal Revenue Service reported that revenues from the tax were more than $250 million shy of expectations in the first half of 2013. The Republican-led House of Representatives passed a tax repeal measure in September, but it never gained traction in the Senate. With Republicans gaining control of the Senate in November, repeal seems a real possibility this year. — Jonathon Shacat, Elizabeth Orr

FDA Clarifies Role of Manipulation In Determining HCT/P Regulation

The U.S. Food and Drug Administration released draft guidance late last month clarifying when human cellular and tissue-based products may be regulated solely under section 361 of the Public Health Service Act and 21 CFR 1271 and when they are regulated as medical devices, drugs or biologics.

For HCT/Ps to qualify under Sec. 361 PHS and 21 CFR 1271, they must be "minimally manipulated" and meant to homologous use only. Their manufacture can't involve the combination of cells or tissues with articles such as water, crystalloids or a preserving or storage agent, and there can be no new safety concerns raised, the guidance says.

The draft defines minimal manipulation of structural tissue and of cells or nonstructural tissue. In the case of structural tissue, minimal manipulation means processing that doesn't alter the "relevant characteristics" of the tissue vis à vis its use in reconstruction, repair or replacement. For cells or nonstructural tissues, it refers to processing that leaves intact the relevant biological characteristics.

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Under the proposed guidance, processing includes any activity other than recovery, donor screening, donor testing, storage, labeling, packaging, or distribution, the guidance explains. Examples include testing for microorganisms, preparation, sterilization, steps to inactivate or remove adventitious agents, preservation for storage and removal from storage. Other activities common during processing include cutting, grinding, shaping, culturing, enzymatic digestion and decellularization, the guidance says.

Processing of HCT/Ps may employ mechanical methods to change the size or shape of the structural tissue. To determine if this alters the original characteristics, firms must assess whether the changes affect the product's use in reconstruction, repair or replacement. Grinding and fragmentation, for example, can qualify as minimal or more than minimal manipulation, depending on the assessment, the FDA says.

Guidance Addresses Modifications

The agency points out that other types of processing — such as chemical modification — can also alter the physical state of a structural tissue.

The draft also gives advice on how to tell whether an HCT/P comprises structural or nonstructural tissue. For instance, a structural tissue characteristic is relevant if it "could have a meaningful bearing on the tissue's utility for reconstruction, repair, or replacement." Examples of relevant characteristics include strength, flexibility, cushioning, covering, compressibility and response to friction and shear.

The guidance, which updates a 2006 document, features an extensive question-and-answer section, including examples of HCT/Ps that are and are not minimally manipulated. PHS Section 361 authorizes the FDA to take steps to prevent the spread of communicable diseases, while 21 CFR 1271 deal with regulation of HCT/Ps.

Comments on the draft guidance are due Feb. 23. View it at www.fdanews.com/12-23-14-HCT-PsGuidance.pdf. — April Hollis

India Eases Foreign Ownership Of Medical Device Companies

Foreigners can now own up to 100 percent of existing medical devicemakers in India without first getting government approval, under a carve-out of the country's foreign direct investment policy for drugs.

The new policy, adopted by the Union Cabinet on Dec. 24, enables companies investing in so-called "brownfield" projects that involve existing facilities to use the same automatic route available for new, or greenfield, investments. Under the old policy, brownfield investments greater than 49 percent of the total budget required prior approval.

The move brings India's foreign direct investment policy for devices in line with the pharma sector and aims to spur investment in the $7 billion sector. According to Department of Industrial Policy and Promotion, FDI in medical and surgical appliances accounted for about US $873,000 between April 2000 and October 2014 — a far cry from the roughly $13 million invested in drugs.

Devicemakers Cool to Proposal

The carve-out creates a new category of "medical and dental instruments and supplies," but does not include a noncompete clause like the one that protects India's generic drugmakers. According to the Cabinet, that clause isn't relevant to the device industry, which is mostly import-dependent.

Indian devicemakers reacted coolly to the news. In a Dec. 25 letter to India's commerce minister, Rajiv Nath, forum coordinator of AIMED, says the trade group supports 100 percent FDI as long as it is restricted to manufacturing and not applied to trading. Granting automatic approval for 100 percent brownfield investments would make India's devicemakers, most of which generate well below $1 million annually, "easy picking" for multinational companies, he adds.

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Rather than expanding FDI, AIMED wants the government to impose a 10 percent import tax on medical devices and reinstate a 4 percent special additional duty, or SAD, to encourage more local manufacturing.

Abby Pratt, vice president of global affairs at AdvaMed, calls the carve-out a "significant step towards creating an appropriate regulatory framework for medical devices" that is separate from drugs. "We are optimistic that the distinction will be taken to the last mile by this government," she tells *IDDM*. — Meg Bryant

FDA Releases 510(k) Transfer Policy: Clarifies Area Previously in Shadow

Companies assuming possession of a previously cleared 510(k) device would have 30 days to register the transfer of ownership on an FDA online database, under draft guidance released late last month.

The proposed policy is intended to end longstanding confusion regarding how to track and update the ownership of 510(k)s.

The FDA does not require a new 510(k) when ownership changes. But while companies typically notify the agency when they acquire a cleared device, establishing an historical sequence of transfers for a particular 510(k) has been challenging, the guidance says.

Implementation of the FDA's Unified Registration and Listing System Device Registration and Listing Module has changed all that, however. An offshoot of the 2007 FDA Amendments Act, FURLS DRLM provides a searchable online database of up-to-date 510(k) information. Devicemakers must register with the database and list the 510(k) numbers for all products they manufacture. When ownership changes hands, the old owner will delist the device and the new one will add its name and information.

If more than one company claims ownership of a 510(k), the FDA will contact all parties involved to determine the rightful owner, according to the guidance. The database will list the last company to enter information as the current owner while the FDA resolves the issue. Court orders, contracts, wills and other historical records may be submitted to support a case of ownership.

Owners of 510(k)s for in vitro diagnostic devices covered under the Clinical Laboratory Improvement Acts should submit updated labeling when the manufacturer or device name changes so that the FDA can ensure the CLIA categorization still applies.

Comments are due Feb. 20 to docket no. FDA-2014-D-1837. View the draft guidance at www.fdanews.com/01-05-15-transfer.pdf. — Elizabeth Orr

U.S.-China Trade Pact Promises Quicker Access to Sino Market

Foreign companies seeking to market novel medical technologies in China should have an easier time, thanks to an agreement by Chinese officials to cut regulatory red tape.

Under the agreement, the China Food and Drug Administration will accelerate reforms of its regulatory review and approval system, including eliminating a device approval backlog within two to three years. The agreement was announced last month at the conclusion of the U.S.-China Joint Commission on Commerce and Trade meeting in Chicago.

Excessively long timelines for getting innovative drugs to market in China is problematic for devicemakers and deprives Chinese patients of important healthcare options and benefits, the U.S.-China Business Council says. According to industry sources, it has taken some companies as long as eight years to get their products on the market.

The trade deal should ease entry for all foreign devicemakers, not just those in the U.S.

Among the expected reforms are measures to allow experimental devices to be tested in China

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while they undergo clinical study in other countries, which should shorten the device's time to market, and clinical trial waivers for applications based on multiregional studies that include data from China, provided the applications comply with technical review requirements.

Negotiators also agreed on language reinforcing plans to expand the list of devices that are exempt from clinical trials in China if they are substantially equivalent to a predicate device — much like the U.S. 510(k) premarket pathway.

AdvaMed praised the deal, saying it would speed products to market strengthening regulatory systems to ensure safety and efficacy.

According to the U.S. Department of Commerce, U.S. companies exported more than $2.7 billion worth of medical devices to China in 2013. — Jonathon Shacat

FDA Proposes Guidance on Radiation Testing Devices

Submissions for radiation biodosimetry medical countermeasure devices should include well-controlled analytical studies establishing device performance across the entire range of the device, the FDA says.

The devices — the majority of which are in vitro diagnostics — are used to measure how much ionized radiation individuals have been exposed to in the wake of a natural or manmade disaster, such as an improvised nuclear device. Some are nucleic acid-based, while others detect changes in protein expression. The Dec. 30 draft guidance applies to RBMCDs submitted either as 510(k)s or PMAs.

Premarket evaluation of these devices is important because radiation resistance varies from patient to patient, making it key that manufacturers explain any differences in natural responsiveness that might lead to accuracy errors. These questions can be established through bench testing or literature review, the FDA says. Manufacturers should also refer to FDA guidance on IVDs and Clinical and Laboratory Standards Institute standards in designing appropriate analytical performance testing.

Benefit/risk evaluations should assess how the RBMCDs' performance differs from that of the laboratory standard, as well as time to results, according to the guidance. Sponsors should provide a detailed description of the device with an intended use statement that specifies the nature of the analyte, the specimen types that can be tested and the specific population for which the test is intended.

RBMCD submissions should also address:

- The stage of response for which the device is intended. For example, submissions on devices meant for early-stage screening and triage should specify the device's output and decisionmaking cut points. Conversely, submissions for devices whose use will be limited to smaller groups may rely more on the assay analytical range and specific clinical indicators of health status, the guidance says;
- Appropriate timeframes for testing. This should include both the beginning and the end of the appropriate testing window; and
- Assay limitations. The FDA wants sponsors to note if validation testing was only performed on certain subpopulations or with specific radiation types. However, every effort should be made to validate the devices with the entire intended-use population.

Animal Studies

While animal data is not traditionally used in IVD submissions, it may be necessary for RBMCDs if human specimens are unavailable, the FDA says. More specifically, animal studies are acceptable if the analyte being detected is not stable in archived specimens, if there are not enough samples in specimen banks for study or if prospective trials would be unethical or yield an inadequate sample size.

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If the device qualifies for animal studies, the submission must demonstrate that the animal model chosen is an adequate substitute for human response. Multiple animal models may be necessary if a single type of animal is not appropriate for all analytes assessed by the device, the FDA notes.

Animal models may also be needed to illustrate whether common drugs, such as antihypertensives or insulin, might interfere with the analytes being studied. Sponsors should also describe any ways in which animal diet and housing may have confounded the results. Finally, experiments should be designed to bridge between animal results and available human clinical information, the guidance says.

Comments on the draft guidance are due March 30 to FDA-2014-D-2065. View it at www.fdanews.com/01-05-15-radiation.pdf. — Elizabeth Orr

Canadian Regulator Updates Advice on Establishment Fees

Health Canada has issued guidance addressing frequently asked questions about medical device establishment licensing and fees.

The FAQ, posted to the agency's website on Dec. 29, discusses important dates for MDELs and fees for any new establishment issued its first license during 2013. The fee is deferred until the end of the first full calendar year of activities under the license.

For example, an establishment whose first MDEL was issued Feb. 1, 2013, would have had its first annual review before April 1, 2014, and the fee and fee remission request fee would have been deferred until Dec. 31, 2014.

The following year, the annual review would again be before April 1 while the fee would be due at time of application and the fee remission request fee would be due with the application, the FAQ explains.

Health Canada will get in touch with establishments that have completed their first calendar year of activities and remind them to pay their fee and submit a fee remission request, if applicable.

The fee for an application submitted during the fiscal year that ends March 31, 2015, is $7,641. This is a flat fee for MDEL application reviews and increases by 2 percent each year.

Companies are eligible for a fee remission if their fees are greater than 1 percent of actual gross revenues from activities performed at the licensed establishment during the previous calendar year. A certified statement of revenue, signed by the firm's chief financial officer, must be submitted in support of such requests.

The FAQ is available at www.hc-sc.gc.ca/dhp-mps/compli-conform/licences/ren-doc/faq-eng.php. — April Hollis

Implant Registries Yielding Solid Outcomes Data, Adjunct to UDI

Patient registries are contributing significant data on the safety and effectiveness of implanted devices, and with the advent of the U.S. FDA's unique device identification system, it is now possible to link implant characteristics to the Global UDI Database, a recent study suggests.

The retrospective study, funded by the FDA, looked at the utility of registries in tracking post-market safety data on patients with orthopedic implants based on research using data pooled by the International Consortium of Orthopaedic Registries. The results were published online in the *Journal of Bone and Joint Surgery*.

Among the findings: patient outcomes did not worsen when a larger-headed hip implant or different plastics — polyethylene and HXPLE — were used; the risk of revisionary survey in patients with large metal-on-metal implants more than doubled compared with patients who had other types of implants; and patients with knee implants that used mobile bearings faced a 40 percent higher revision rate than patients whose implants used fixed bearings.

According to the authors, the ICOR database of clinical attributes and characteristics, which assigns a catalog number to each implant, serves as a useful adjunct to the FDA's GUDID. Any modification in

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design of the implant prompts a new catalog number. However, the study notes, "there has been no worldwide consensus on the encoding of part numbers, and, in some instances, different devices have been identified with the same catalog number, and different numbers have been used for the same implant, depending on where it was being sold."

Even so, 99 percent of implants are correctly identified using the ICOR system, the authors add. "As UDI is implemented, the registries will also link implant characteristic to the UDI database," increasing its value for researchers and practitioners.

"The ability to create an international, distributed research network for medical devices is unprecedented and opens new opportunities for the development of investigations of comparative effectiveness and device safety," the authors say. They believe the approach could be used to track the safety and performance of other types of implants and surgical devices.

The study was a collaborative effort of Kaiser Permanente, Weil Cornell College of Medicine in New York and seven national, regional and payer registries. It is available at http://jbjs.org/content/96/Supplement_1/1. — Elizabeth Orr

Spanish Devicemaker Warned On Environmental Procedures

DIMA, a maker of slings and incontinence mesh, received an FDA warning letter for insufficient environmental controls and other GMP slips.

The Calatayud, Zaragoza, Spain, devicemaker failed to validate that its clean rooms operate within specifications, according to the Oct. 15 letter posted online Dec. 30. The company shuts down its clean rooms overnight and then has a waiting period after startup each morning, but did not validate the rooms after the waiting period.

The letter also raps DIMA for failing to update its risk analysis after it made a design change to the Contasure Needleless Mess Kit. The design and development procedure also lacked requirements for risk analysis or for identifying acceptance criteria for design validation activities.

While DIMA conducted design validation activities for two projects, there were no documented acceptance criteria to show that devices conform to defined user needs and intended uses, the letter says.

At the time of the June 30 to July 3, 2014, inspection, DIMA had no procedures for handling changes to a specification, method, process or procedure. The company installed a new part on its weaving machine in response to a high number of rejections, but did not document that this change was verified or validated before implementation.

The devicemaker also had no documentation for the installation and operational qualification of its Computer Numeric Controlled machine, which was installed and tested by machine's manufacturer.

DIMA's corrective and preventive action procedure did not identify the actions needed to correct and prevent recurrence of quality problems. And the company had not implemented and recorded corrective actions for retraining, despite identifying that as a corrective action.

Meanwhile, DIMA opened a CAPA after receiving a complaint that the monofilament in a Surelift Anchor broke during surgery and determined that corrective actions were not needed. However, the justification was not documented.

Finally, DIMA's nonconforming product procedure did not require it to document the disposition of nonconforming products.

DIMA could not be reached for comment by press time. The warning letter is available at www.fdanews.com/12-30-14-DIMA.pdf. — April Hollis

Supplier Qualification Surveys Should Be Comprehensive, Revealing: Expert

Ensuring that product components and supplies are of top quality and delivered on time is key to running a successful business, and supplier qualification surveys need to be sufficiently broad to ensure a good result, an industry expert says. Among the topics every survey should include are inspection procedures and procurement and document controls.

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Jeff Kasoff, director of quality at Medivators, begins his surveys by asking suppliers for their U.S. FDA or Health Canada registration information, if applicable, and whether they are ISO-certified. If the supplier or contractor is not ISO-certified, they must complete the remainder of the survey.

Kasoff's survey includes a wide range of questions, beginning with organizational specifics such as a chart showing the relationship between quality and manufacturing. Then there are questions about site size, the percentage of the site that is dedicated to manufacturing, environmental issues, pest controls and more.

Survey Should Assess Quality System

The survey should also look at the supplier's quality program and quality system, Kasoff says. "I want to see if they have any sort of quality planning function. Do they have a quality manual or something like that? Do they perform a training?" He discussed supplier qualification at a recent FDAnews webinar.

Evaluations of audit planning and procedures should include the supplier's standard inspection document and their procedure for performing an inspection. For incoming inspections, the survey should assess the rate of rejections, documents used by the supplier and product statuses.

The survey should also look at procurement control, determining how the supplier specifies the components they purchase and how they will verify that they received the correct components.

Kasoff also asks for production qualification, "another example of something that they may not have," he says. "How do they know that the process they're using is one that results in product that meets my requirements?"

In-Process Inspection

While in-process inspection is not required, it can be very useful, Kasoff adds. "If my supplier tells me four-week delivery and they don't perform any in-process inspection, but they do perform a finished device …final inspection, they're going to call me at 3.5 weeks and say, listen, Jeff, we've got some really bad news, none of that product is good." With in-process inspection, any problems would be caught early on.

Other points to cover in supplier qualification surveys include design and document, finished product handling, calibration and maintenance, complaint handling and returns.

At the end of the survey, the supplier receives a rating of acceptable, conditionally acceptable or unacceptable. Kasoff recommends retaining the records of suppliers that don't make the cut. "These are helpful to show the FDA the process for weeding out unacceptable suppliers," he says.

Occasionally, Kasoff runs into suppliers that appear legitimate but refuse to complete the survey. To these he gives a 12-month conditional status, making sure that purchasing and quality assurance staff document that determination. Once the trial period is up, if the supplier's performance and history are both acceptable, the rating is upgraded to "approved." — April Hollis

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