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AdvaMed Takes Issue With FDA Guidance On Humanitarian Device Exemption

AdvaMed said it strongly supports the FDA's efforts to provide clarity around "probable benefits" from marketing authorizations for humanitarian use devices, but the association said the guidance needs to make it clear that randomized clinical trials are not needed to demonstrate probable benefit.

This is especially true for pediatric populations where randomization can be ethically challenging, AdvaMed said.

As mandated in the 21st Century Cures Act, the FDA issued draft guidance to clarify the agency's rules on humanitarian device exemptions under the act. The agency said it would consider the target patient population, size, intended use and current treatment options in assessing devices for the HDE program.

(See **Guidance**, *Page 2)*

FDA Issues Draft Guidance On Export Certificates for Devices

The FDA released a new draft guidance on its review process for a Certificate to Foreign Government (CFG) and listed the reasons it may deny a request.

Some reasons for a denial include an injunction or seizure action under the Food, Drug and Cosmetic Act, a Class I or Class II recall, or if an establishment violates good manufacturing practices.

In case of a denial, the agency will notify the requestor in writing and identify the finding that serves as the basis for the denial. In cases where the denial is specifically because of a facility's noncompliance with GMPs, the agency will also provide a "substantive summary" of the GMP failures identified.

Anyone who receives a CFG denial may request a review so they can present information about actions taken to address the reason for the denial, the agency said.

(See **Certificates**, *Page 2)*

Guidance, *from Page 1*

To qualify for the program, devices should be intended for treatment or diagnosis of conditions affecting a maximum of the Cures Act's limit of 8,000 U.S. patients.

The association took issue with the FDA's position on what may be considered valid economic factors to determine profit eligibility, because pediatric populations are typically broadly geographically dispersed, making trial recruitment challenging.

This would mean that companies would be discouraged from "even considering the HDE pathway, particularly if profit is prohibited," AdvaMed said in its comments to the agency.

"As just one example, one company incurred costs of $15 million for a 40-person pediatric study at 15 sites," AdvaMed said, urging the FDA to allow economic considerations to be a factor.

It suggested striking language from the draft guidance that said the FDA should not consider economic factors as a basis for pediatric trials being "impossible" or "highly impracticable."

FDA Approval Clarification

AdvaMed agreed with the FDA's language in the draft guidance that makes clear approval of an HDE is considered "FDA approval" of the device, and the device is no longer considered investigational.

Comments noted that private insurers typically refuse to reimburse for pediatric humanitarian use devices, as the statute requires that HUDs can only be administered in facilities with functioning IRBs.

Under the 2017 FDA Reauthorization Act, an institutional review board or "appropriate local committee" can issue an approval. A local committee qualifies if it is a standing facility committee that has "expertise and experience in reviewing and making treatment decisions for clinical care, particularly in applying innovative medical device technologies to clinical care," according to the draft.

"Our members reported that for most HDEs, obtaining reimbursement is a significant undertaking for the physician, hospital, patient and manufacturer, requiring multiple prior authorization requests, appeals and conversations with insurer medical directors, and that process can take several months," the association said.

Read the full comment here: www.fdanews.com/08-16-18-AdvaMed.pdf.

Certificates, *from Page 1*

CDRH's exports branch and CBER's import and export staff "will make every effort to directly resolve issues," but if they don't resolve the issue "each Center's review process will be followed," according to the draft guidance.

Read the full draft guidance here: www.fdanews.com/08-17-18-Guidance.pdf. — Zack Budryk

FDA Proposes to Define Certain Device Accessories as Class I

The FDA issued a list of medical device accessories that it believes are safe and effective enough to be categorized as Class I and requested public feedback on the proposed list.

Class I devices are subject to the least amount of control because the agency believes their use presents a "low to moderate risk."

The accessories the agency has proposed to be considered distinct from other devices and classified into Class I are:

- Gastroenterology-urology accessories to a biopsy instrument;
- Penile implant surgical accessories;
- Ureteral stent accessories;
- Biliary stent, drain and dilator accessories;
- Suprapubic catheter accessories;
- Implanted mechanical/hydraulic urinary contingence device surgical accessories;
- An air-handling apparatus accessory; and
- A corneal inlay inserter handle.

The FDA said it has not made a final determination for the suggested accessories and called for comment on the list.

Read the notice here: www.fdanews.com/08-16-18-ClassI.pdf. — James Miessler

Gottlieb Highlights Commitment To New Pediatric Devices

FDA Commissioner Scott Gottlieb said the agency wants to encourage the development of medical devices designed specifically for pediatric patients and noted "there are still far too few devices on the market designed specifically to treat, diagnose, or cure diseases in children."

Over the past decade, despite legislation from Congress and regulatory process improvements by CDRH, the number of novel medical devices designed, evaluated, and approved for pediatrics is only about a quarter of those for adults and the majority of pediatric approvals are not for children under 18 years of age, Gottlieb said at an Aug. 13-14 public meeting on pediatric device development at the agency's White Oak campus in Silver Spring, Maryland.

In 2017, the agency approved 66 devices through the premarket approval and humanitarian device exemption pathways but only 18 of

(See **Gottlieb***, Page 4)*

BRIEFS

Health Canada Opens Consultation On 'Pause the Clock' Proposal

Health Canada is seeking feedback on its plan to "pause the clock" during reviews of medical devices under specific circumstances.

The mechanism would help sponsors meet review deadlines and clarify any issues that arise without incurring penalties. It would also help hold the department accountable only for the time it spends on a particular submission or application.

The mechanism would be implemented only for specific circumstances that would not normally arise under the review process.

For example, Health Canada would be able to pause the clock for medical device applications linked together that have different review times, or for a sponsor's extension request. The department would also be able to pause the clock when it seeks advice from expert panels during reviews.

Malaysia Extends Device Labeling Deadline by Three Years

Malaysia's Medical Device Authority is pushing back device labeling requirements to allow for a three-year transition period to give device-makers more time to meet the new requirements.

Previously, a two-year transition period was to apply beginning in 2016. Manufacturers will now have until 2021 to meet the new labeling requirements, which were to be in effect beginning in 2018.

The Aug. 5 MDA notice said that existing labeling will apply during the transition period.

The new labeling requirements coincide with new device registration requirements for importing, exporting, or placing medical devices on the market (*IDDM*, March 28).

Australia Issues Update on AERs Attributed to Bayer's Essure Device

Australia's Therapeutic Goods Administration released an update on Bayers's Essure contraceptive device, saying the agency received 59 adverse event reports relating to women implanted with the device since it was supplied in Australia in 1999 until Aug. 6.

TGA removed the device from the Australian Register of Therapeutic Goods on Feb. 9.

The AERs included changes in menstrual bleeding, unintended pregnancy, chronic pain, perforation, migration of the device, and allergy/hypersensitivity or immune-type reactions. Surgery was required in some instances to remove the device, the TGA said.

The TGA said that although no new Essure devices were supplied for the Australian market after May 31, 2017, some devices were already in the supply chain and were used until they were recalled in August 2017. The device was not supplied again in Australia following the recall.

In September 2017, Bayer advised the TGA that it would not be seeking EU recertification for the device.

TGA Offers New Guidance On Electronic Instructions for Use

Australia's Therapeutic Goods Administration issued new guidelines on electronic instructions for use for medical devices.

Current Australian regulations require all medical devices to include a label and instructions for use and, where applicable, a patient implant card and information leaflet.

Only devices intended for professional use are eligible for electronic instructions for use (eIFU), according to the TGA, whereas devices supplied to the general public and in vitro diagnostics must include a paper copy of the IFU.

The eIFU may be supplied in several formats, including a graphical user interface (GUI) or a help system, and may be stored on portable electronic media or the manufacturer's website.

The eIFU provided to the TGA must state its release date and target regulatory jurisdiction as well as documenting version history.

Manufacturers should continue providing obsolete versions of the IFU for the benefit of users with older versions of the device.

Manufacturers must make eIFUs available on their websites easy to navigate and search and not require users to create an account to access them, the agency said. — Zack Budryk

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Gottlieb, *from Page 3*

those were indicated for use in a pediatric population. Of the remaining 48 approvals indicated for adults, 42 were determined by internal pediatric experts to have the potential to treat, diagnose or cure a disease which occurs in a pediatric subpopulation.

Gottlieb cited challenges and "practical roadblocks" surrounding the development of pediatric medical devices. "One issue is the obvious – there are physical differences between children and adults that can affect development. There are also higher costs sometimes associated with development of medical devices for any affected population of a small size, and especially those designed for a pediatric market.

He said the agency is increasing the number of medical devices with labeling for pediatric patients by incorporating known information about device effects in other populations to support pediatric indications.

It is also recruiting pediatric experts for FDA advisory panels whenever there is a reasonable likelihood that the device will be used for children.

In addition, the agency is collecting data on the unmet needs for pediatric medical devices and the barriers to the development of new pediatric devices and is taking new steps to protect children who participate in clinical trials, he said.

GEM City Engineering Cited For Document Controls

A litany of major GMP deficiencies — ranging from inadequate document control procedures, CAPA, device acceptance procedures and procedures to control product — plagued GEM City Engineering and Manufacturing during a Feb. 21 to March 1 FDA inspection of its Dayton, Ohio facility.

The eight-item 483 cited numerous examples of the contract manufacturer's faulty document control procedures. For example, document changes didn't include a valid signature of the person approving the change, and procedures referenced documents that were not approved. The CMO's supplier survey for its medical device metal supplier included a checklist that was not defined in the procedures, the 483 said.

Corrective and preventive action procedures were found lacking because none of the corrective action reports reviewed included a verification or validation prior to closing the corrective action reports.

A corrective action reported was initiated for deficiencies in process validation and included an action item to "write IQ, OQ, PQ procedures for our ISO 13485 Quality System." However, the director of Quality and Continuous Improvement told the investigator there were no approved procedures for process validation "other than what is defined in their quality manual."

At least 15 corrective action reports between May 2016 and October 2017 did not include any objective evidence or supporting documentation for corrective actions taken, the agency said.

(See **483***, Page 6)*

Staffing an Audit

A critical factor in successful auditing is having the right people conduct the audit, meaning individuals with the right mindset and training to ensure that the audit process is rolled out effectively.

Some larger corporations may have full-time auditors who handle all audits throughout company facilities; in that case, a big challenge is hiring and retaining qualified people. But it's far more common for companies to have part-time auditors picked from among key staff, and it's important to remember that the auditing duties will take away from the audit team's "real" jobs, so planning to balance work responsibilities can be a challenge.

Employees who perform audit duties in addition to their regular jobs should have the audit responsibilities, including training requirements, included in their official job descriptions. Auditors can come from departments other than quality and regulatory, but it is also important to make sure that part-time, in-house auditors be chosen because auditing is truly a reasonable part of their jobs.

Another option for some devicemakers may be to leverage auditors from corporate resources, or from a sister or parent company. This can be a good option from the perspective of ensuring the independence of the auditors and benefits of bringing in fresh eyes who are not involved in the day-to-day operations.

Susan Reilly, owner of the consultancy Reilly & Associates, cautioned against assuming that a mandated corporate audit — when corporate policies say that a business unit or facility will be audited at a particular frequency — will count as an internal audit for regulatory purposes.

"[These] are typically not viewed as an internal audit by either FDA or by your ISO registrar because it is a mandated corporate rather than one of your internal audit requirements," she explained.

One way devicemakers can ensure truly independent audits is to hire outside consultants or contractors who specialize in device manufacturing audits, but this option is a more costly than relying on internal or corporate resources. Reilly noted that she has seen some smaller companies located near to each other enter agreements whereby they audit each other, which offers similar benefits to a professional auditing contractor without the cost.

Excerpted from the FDAnews management report: *Effective Internal Audits and Quality Control Units for Devicemakers*.

Wheelchair Maker Permobil Fails To Establish Adequate CAPA

Failure to implement corrective and preventive actions and to control nonconforming product landed wheelchair maker Permobil a 483 following a January inspection of the company's Lebanon, Tennessee, plant.

The company apparently held a meeting in September 2017 to open a CAPA, but it was not actually opened until January 2018.

The FDA said the firm's non-conforming product procedure was inadequate in that it didn't ensure investigations were adequately completed or documented.

The facility also failed to define how the disposition of nonconforming product would be documented and it didn't describe which routine rework activities could be completed without rework forms.

Read the Permobil Form 483 here: www.fdanews.com/08-16-18-permobilinc483.pdf.

Alliance Precision Plastics Cited For Lack of Written Procedures

Failing to establish procedures to review and evaluate complaints as well as CAPA procedures landed Alliance Precision Plastics a six-item FDA Form 483 following a March 28 to 30 inspection of its Rochester, New York, facility.

Alliance's CAPA procedures didn't include requirements to verify or validate corrective actions to ensure they don't adversely affect the finished device. The firm does custom injection molding and mold design as well as contract assembly for original equipment manufacturers.

The firm's procedure for customer complaints did not gather enough detail to ensure they were processed in a uniform manner. For example, the procedure didn't include requirements to document the complainant's name, address, phone number or the nature and details of the complaint, results of an investigation, device identification or any reply to the complainant, the agency said.

The inspector found the firm had not established written medical device reporting procedures or procedures to adequately control produce that did not conform to specified requirements.

For example, a number of nonconformances failed to document the lot number of the affected products, and the nonconformance "did not have a documented root cause as required by the firm's procedures."

Software used as part of the quality control system was not adequately validated for its intended use, the inspection revealed. The software was used to perform dimensional analysis on speculum components to ensure they meet specified requirements before being released for assembly.

The FDA also cited the firm for not establishing schedules for adjusting, cleaning and maintaining equipment. The 483 notes that preventive maintenance performed on injection molding machines was not included on the firm's preventive maintenance schedule.

Read the Alliance Precision Plastics Form 483 here: www.fdanews.com/08-16-18-alliance483.pdf.

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The contract manufacturer failed to develop production processes that ensured devices conformed to specifications, and production procedures don't define the manufacturing steps to assemble the SAF-T-Pump device, the FDA said. In addition, there were no procedures that defined acceptance criteria, including test methods for the device.

The FDA said that GEM City Engineering hadn't documented complaints in the last two years, and it did not have procedures in place to adequately control nonconforming products. It also had not established procedures for device history records, and it did not document or approve the validation of the machines used in manufacturing medical devices.

Read the Gem City Form 483 here: www.fdanews.com/08-16-18-gemcity483.pdf.

FDA Clears First App For Contraceptive Use

The FDA said it would permit marketing of Nordic AB's mobile medical application Natural Cycles for use as a method of contraception.

The app received de novo clearance as a stand-alone software application, intended for women 18 years and older, to monitor fertility.

The device includes an algorithm that analyses patient-specific data, such as temperature and menstrual cycle dates to distinguish between fertile and non-fertile days and provides recommendations related to contraception.

The clearance was supported by clinical trials that involved 15,570 women who used the app for about eight months. It had a "perfect use" failure rate of 1.8 percent, which means 1.8 women who used the app for one year will become pregnant because they had sexual intercourse on a day when the app predicted they would not be fertile or because their contraceptive method failed when they had intercourse on a fertile day, the FDA said.

As part of the de novo clearance, the FDA is establishing special controls that clarify expectations in assuring accuracy, reliability and effectiveness. Subsequent devices with the same intended use would go through the FDA's 510(k) process by demonstrating substantial equivalence.

APPROVALS

FDA Approves First EpiPen Generics

The FDA approved the first generic versions of Mylan's EpiPen and EpiPen Jr., giving Teva permission to market its generic epinephrine auto-injector in 0.3mg and 0.15mg strengths.

FDA Commissioner Scott Gottlieb said the approval is part of FDA's "longstanding commitment to advance access to lower cost, safe and effective generic alternatives once patents and other exclusivities no longer prevent approval."

Teva did not immediately disclose the prices of the new products.

Avita Gets Expanded Compassionate Use for Burn Treatment Device

The FDA approved a large increase in the number of patients who may use Avita's Recell autologous cell harvesting device, used for severe burns, under a compassionate use investigational device exemption (IDE) program.

With the approval, up to 108 patients suffering from severe and life-threatening burns may be treated with the Recell device and up to 26 U.S. burn centers may participate.

The compassionate use IDE program allows patients to be treated with the device before it receives FDA approval.

Caretaker Medical Receives CE Mark for Vital Signs Monitor

Caretaker Medical successfully received a CE Mark for its wearable, wireless vital signs monitor.

The continuous non-invasive "beat by beat" blood pressure and wireless vital signs monitor was already approved by the FDA.

The device measures blood pressure, heart rate, SP02 and body temperature and does not use external arm cuffs or arterial catheters.

FDA Rejects Endobronchial Coil System for Treating Severe Emphysema

Elevair's premarket approval (PMA) application for its endobronchial coil device was shot down by the FDA.

The coil system is meant to reduce lung volume and hyperinflation by applying compression to damaged tissue and helping the lungs regain elastic recoil.

The device is designed to treat severe emphysema using a minimally invasive, bronchoscopic technique to place memory coils in the patient's lungs.

(See **Approvals***, Page 8)*

Approvals, *from Page 7*

NetScientific Receives CE Mark for Immunoassay

NetScientific earned a CE Mark for its ProteaseTag active Pproteinase-3 immunoassay and announced its firm commercial sale to a US biotech company.

The immunoassay is designed for clinical researchers investigating chronic respiratory conditions, such as cystic fibrosis, bronchiectasis and chronic obstructive pulmonary disease, in both commercial and academic areas.

7D Surgical's Cranial Module Device Receives FDA Approval

The FDA granted 510(k) clearance for 7D Surgical's machine-vision image guided surgery (MvIGS) system for use in cranial surgery.

The device uses machine vision algorithms and camera-based tech to acquire virtual fiducial markers from the patient's anatomy, allowing for cranial registration in nearly any surgical position.

It can also register multiple datasets to visualize the patient's anatomy using many types of medical imaging.

FDA Grants 510(k) Clearance To BioSig's Cardiac Signal Device

BioSig Technology's Pure EP System, a medical device that measures, records and displays high fidelity cardiac signals, received 510(k) clearance from the FDA.

The device is intended for use in an electrophysiology (EP) laboratory to provide visualization tools that can help to analyze a patient's intracardiac and electrocardiographic signals during EP procedures.

The computerized system is non-invasive and can potentially increase the diagnostic value of the signals, improving EP study accuracy and efficiency. It is indicated for use by licensed healthcare practitioners who interpret the data.

Procleix's Zika Assay Earns FDA Approval for Use With Panther System

The FDA approved Procleix's Zika virus assay for blood screening on Procleix's Panther system.

The assay is approved for detecting the Zika virus in donated individual or pooled plasma specimens, making it useful for blood banks in their efforts to screen blood donations for the virus.

It is also approved to test plasma or serum samples to screen other living or dead organ donors and human cells, tissues and cellular and tissue-based products.

Inova Diagnostics' Assay Cleared by FDA

The FDA granted clearance to Inova Diagnostics' Quanta Flash HMGCR, a marker that helps to diagnose idiopathic inflammatory myopathy, a group of disorders that involve the inflammation of muscles used for movement.

The assay is one of thirty others cleared by the FDA for use on the Bio-Flash device, a random access chemiluminescent analyzer used in autoimmune laboratories.

Inova's test can help distinguish between patients with self-limited myopathy who will likely recover and patients who are at severe risk of illness and often need aggressive immunosuppressive therapy.

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Customer Service
(888) 838-5578 • +1 (703) 538-7600
customerservice@fdanews.com

Editorial: Declan Conroy
+1 (703) 538-7644
dconroy@fdanews.com

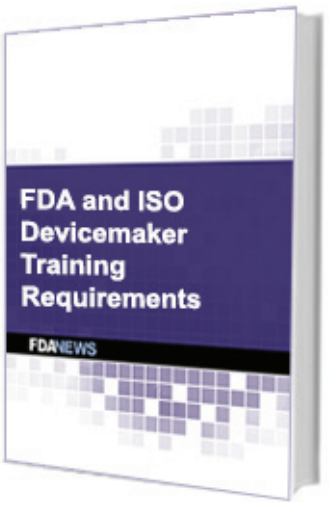
Ad Sales: Jim Desborough
+1 (703) 538-7647
jdesborough@fdanews.com

Multi-User Sales: Jeff Grizzel
+1 (703) 538-7669
jgrizzel@fdanews.com

300 N. Washington St., Suite 200 • Falls Church, VA 22046-3431 • Phone: (888) 838-5578 • +1 (703) 538-7600 • www.fdanews.com

Reporters: Zack Budryk, James Miessler, Bill Myers

President: Cynthia Carter



FDA and ISO Devicemaker Training Requirements

Device manufacture is a complicated business, but few areas are more rulebound than QMS. Many a devicemaker has come up short trying to stay abreast of the FDA's QSR, ISO 13485:2016, and other ISOs while trying to comply with competence, training and awareness rules.

It takes more than teaching simple skills to achieve the state of job readiness and performance required of devicemakers' workforces. Regulators agree that a comprehensive training program should consider employee education, experience, background and skills. What they don't agree on is what those concepts mean and how to incorporate them into training.

FDA and ISO Devicemaker Training Requirements breaks down training requirements in both the FDA's QSR and international standards ISO 13485, 9001 and 10018 — among others — shows where they overlap and where they differ and provides a plan for developing a training program that fills in all the gaps. You will learn:

- The four elements of competency
- Definitions of key terms and requirements
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