INTERNATIONAL DEVICES & DIAGNOSTICS MONITOR

Vol. 4, No. 22
May 28, 2018

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World Health Organization Releases First List of Essential Diagnostics

The World Health Organization released its first-ever list of essential diagnostics that will aid countries in selecting more accurate tests to detect diseases.

Like the established Essential Medicines List, which has been in use for four decades, the Essential Diagnostics List is intended to provide evidence-based guidance, and set reference materials for developing national lists of essential in vitro diagnostic tests.

National essential medicines lists have been successful in raising awareness, guiding procurement and regulation policies and facilitating access to affordable medicines, particularly in low-resourced countries, by prioritizing the most important medicines all countries need to make available to their populations.

WHO anticipates that national essential diagnostics lists will provide similar benefits and improve access to essential IVDs.

The diagnostics list was developed following an extensive consultation. The draft list was reviewed by WHO's Strategic Advisory

(See **WHO**, *Page 2)*

EC Updates Manual on Borderline And Classification for Medical Devices

The European Commission provided further guidance for devicemakers on how to distinguish borderline devices and in vitro diagnostics in a new Version 1.19 of its manual on borderline and classification for medical devices.

The manual notes that borderline cases can occur when it is unclear whether a product is a device, an in vitro diagnostic, an active implantable or not, so it is difficult to apply the classification rules of the Medical Devices Directive.

Different interpretations can occur among EU member states, the Commission said, noting the manual is a result of discussions of borderline and classification meetings among regulators to

(See **Manual**, *Page 4)*

WHO, *from Page 1*

Group of Experts on In-Vitro Diagnostics (SAGE IVD). The SAGE IVD made recommendations for the content, format and implementation of the first EDL.

The list of 113 products concentrates on in vitro tests, with 58 tests listed for detecting and diagnosing a wide range of conditions. The remaining 55 tests are designed to detect, diagnose and monitor "priority" diseases such as HIV, tuberculosis, malaria, hepatitis B and C, human papillomavirus and syphilis.

Some of the tests are particularly suitable for primary health care facilities, where laboratory services are often poorly resourced and sometimes non-existent, such as tests to rapidly diagnose a child for acute malaria or glucometers to test for diabetes. An estimated 46 percent of adults with Type 2 diabetes worldwide are undiagnosed.

"Our aim is to provide a tool that can be useful to all countries, to test and treat better, but also to use health funds more efficiently by concentrating on the truly essential tests," said Mariângela Simão, WHO's assistant director-general for access to medicines, vaccines and pharmaceuticals. "Our other goal is to signal to countries and developers that the tests in the list must be of good quality, safe and affordable."

For each category of test, the EDL specifies the type of test and intended use, format, and if it is appropriate for primary health care or for health facilities with laboratories. The list also includes links to WHO guidelines and prequalified products.

WHO plans to update the EDL regularly and it will issue a call for applications in the next few months to add categories to the next edition. The list will expand significantly over the next few years as it addresses other key areas including antimicrobial resistance, emerging pathogens, neglected tropical diseases and additional non-communicable diseases.

Read the list here: www.fdanews.com/05-22-18-WHODxlist.pdf.

BRIEFS

FDA Approves Marketing AI Technology To Help Diagnose Wrist Fractures

The FDA signed off on the marketing of an artificial intelligence program for easier detection of wrist fractures.

Imagen's OsteoDetect uses an AI algorithm to analyze wrist X-rays in a variety of environments.

The FDA reviewed OsteoDetect through the De Novo premarket review pathway for low-to-moderate-risk devices.

Roche Recalls Additional Accu-Chek Test Strips That Produce Biased Results

Roche recalled another of its Accu-Chek glucose meter test strips because of faulty readings.

The company said that in rare cases, the Accu-Chek Inform II test strips can report values that are too high or too low, despite the meter's fail-safe design. The same issues have also been detected in lots of the company's Accu-Chek Performa and Accu-Chek Aviva devices.

The company said it investigated the root cause of the issue and has begun implementing corrective measures.

Health Canada Begins Transition to Global Medical Device Nomenclature

Health Canada is changing how it categorizes medical devices and adopting the Global Medical Device Nomenclature (GMDN).

The GMDN lists generic names used to identify medical device products, to enable effective monitoring by regulators and expedite the exchange of information between jurisdictions. The growing GMDN database is made up of over 23,000 active terms that cover all major technologies and intended uses.

Health Canada will issue manufacturers a list of medical devices associated with active medical device licenses and give them the opportunity to determine the 5-digit GMDN code for their devices.

"Continuous and significant technological advancement in the field of medical devices makes it necessary for Health Canada to implement a nomenclature designed to keep pace with medical devices innovations," the agency said.

The department is also updating its forms for medical device license applications and license amendments, and it will ask applicants to provide their GMDN data for the new applications.

Although the agency may contact manufacturers for clarification on incorrect codes, it said this will not delay application processing.
— James Miessler

UK's MHRA Releases First Year of Brexit Plan

The UK's Medicines & Healthcare products Regulatory Agency released a business plan for 2018-2019, covering the first year of the agency's five-year plan for operating post-Brexit.

MHRA said it will continue to serve as a full-service regulator, acting as a competent authority for medical devices and monitoring the performance of notified bodies.

The agency will ensure that all legislation is transposed into UK law by March 30, 2019. National IT portals and databases will continue to operate, and they will be flexible enough to allow information exchange with EU portals. The agency also plans ongoing participation in the EU regulatory network, committees and working groups.

It is continuing to prepare for the implementation of the new EU Medical Device Regulations and IVD Regulations "subject to EU exit, including identification of specific organizations affected, enhanced communications plan and quantification of the additional workload for MHRA of new regulations."

In addition, the MHRA will work with the UK government and healthcare organizations to expand use and future capability of UK healthcare datasets and data capture systems for medical devices to widen and strengthen the use of real world evidence.

At the same time, the agency will launch a new version of its Central Alerting System and it will establish a process for assessing parallel import applications that use a centrally authorized reference product.

The agency plans on expanding its international work by establishing an international office to support global outreach with organizations like the International Medical Device Regulators Forum. For example, it plans on working with IMDRF partners to develop medical device adverse event terminology and encourage its use within new international data standards. MHRA also will continue to lead the development of the EU's first Periodic Safety Update Report within the new EU MDR to be implemented in 2020.

Expanding AI

Innovation will continue to be a focus, with MHRA supporting development of personalized medicine and companion diagnostics. It plans to

develop expertise in using artificial intelligence to maintain the pace of regulation in this rapidly growing area. Along these lines, it hopes to provide real-time benefit risk information to support patients' and healthcare professionals' decisions by using a wide range of data sources and digital systems and tools.

(See **MHRA***, Page 4)*

Global Medical Technology Alliance Adopts Ethics Principles

The Global Medical Technology Alliance adopted harmonized ethical business principles across the association's member associations.

Representing 26 international and regional medical technology associations, including AdvaMed, GMTA members committed to upholding common principles regarding: consulting arrangements; support for third-party educational programs; company-organized training and educational events; sales and promotional meetings; educational and promotional items; entertainment; charitable donations; demonstration and evaluation products; ensuring effective implementation; and third-party sales and marketing intermediaries.

"GMTA's adoption of these principles represents the culmination of AdvaMed's longstanding work with fellow GMTA members around the world to achieve global harmonization of ethical business principles in the medical technology industry," said Scott Whitaker, president and CEO of AdvaMed.

MHRA, *from Page 3*

Goals for this year include:

- Completing delivery of IT systems and processes for device registrations, as well as re-engineering processes for Devices Safety & Surveillance and Information & Operations;
- Continuing work to generate sustainable devices funding, including assessing charging in other EU countries and refining models to cover all contingencies for the UK's exit of the EU;
- Working with the Department for Health and Social Care (DHSC) and partner organizations to understand the implications for MHRA's regulatory scope of AI, apps, and current cyber security risks and emerging threats; and
- Developing cyber "resilience."

Read the MHRA business plan here: www.fdanews.com/05-16-18-MHRAbizplan.pdf.

Manual, *from Page 1*

provide feedback on products that have raised doubts or concerns.

The manual includes recent decisions on whether certain products claimed by the manufacturer to be medical devices or IVDs actually qualify as medical devices or IVDs under the new regulations.

For example, a light box indicated to treat seasonal affective disorder (SAD) was deemed to be a medical device. However, the equipment used for pharmacy compounding was deemed not to be a medical device.

Similarly, a thermomixer intended to control the temperature of and to mix liquids for preparing and processing samples for IVD applications, were not considered IVDs or medical devices.

In recent decisions, rugby helmets, autopsy saws, UV flow germicidal lamps, water filters, bone void fillers containing animal growth factors, weight management products were deemed not to be medical devices, while whole body and partial body cryotherapy chambers qualified as medical devices.

The manual provides guidance on whether certain borderline IVDs would in fact qualify as IVDs under the IVD Directive, including decisions for CE-labeled microscope slides, channel pipettes and fluid collection bowls.

Certain solutions or medicines can be considered medical devices when they are used for the purpose of diagnosis or to control conception, so in-vitro fertilization and assisted reproductive technology products qualify as medical devices. However, peritoneal dialysis solutions do not qualify as medical devices.

Agents for transporting and storing organs intended for transplant are considered medical devices and creams containing zinc oxide qualify as medical devices but hand disinfectants do not.

Devicemakers can review the new manual to get a sense of the European regulators' current thinking and how they may deal with other borderline cases.

Read the EC manual here: www.fdanews.com/05-22-18-ECmanual.pdf.

Medegen Racks Up 13-Item Form 483 For Quality System Failures

A January inspection of Gallaway, Tennessee-based device manufacturer Medegen Medical Products by the FDA uncovered a range of quality system failures, including a serious lack of process controls for which the firm received a 13-item Form 483.

The firm's injection molding process used to produce medical devices was not validated, nor was the sterilization process for sterile products.

The investigator observed that process control procedures "that describe any process controls necessary to ensure conformance to specifications have not been adequately established."

For example, the firm used "untitled and uncontrolled documents as a guide for setting up injection molders" and to manufacture three-gallon sharps containers, the agency said. "You have not established procedures that define the control of this process and during the inspection you stated that you routinely deviate from the parameters defined in the untitled document," the agency said.

In addition, the facility lacked procedures for final acceptance testing, and a review of device history records indicated that products that did not meet specifications were accepted and there was no documentation when a nonconformance was later found.

None of the 16 complaint records reviewed included documentation that the complaint was evaluated for MDR reportability and none of the complaint records included documentation of an investigation or record of why no investigation was made.

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

QSR-Compliant Equipment Control

Devicemakers must ensure that all equipment used in the manufacturing process meets specified requirements and that it is all appropriately designed, constructed, placed, installed, maintained, adjusted, cleaned and used.

Each of those steps warrants attention, from ensuring that outside suppliers provide equipment that is fit for purpose and meets regulatory requirements through placing and installing the equipment appropriately for its use and ensuring the equipment is regularly maintained, adjusted and cleaned in accordance with FDA expectations.

Under QSR, devicemakers' responsibilities include:

- Identifying the requirements for each piece of equipment;
- Evaluating and selecting suppliers and using purchasing data to illustrate that a supplier's equipment meets requirements;
- Developing a design methodology and construction specifications for all internally constructed equipment, including how to appropriately place and install the equipment;
- Providing a specification document to show that internally constructed equipment is appropriately designed and built;
- Determining maintenance requirements, including access to lubrication, filters and adjustments; and
- Accounting for human factors and safety in operation methods.

QSR also requires devicemakers to determine if deviations from product specifications could occur in the manufacturing process and, if so, establish and maintain process control procedures to prevent that from happening. To ensure compliance, devicemakers must conduct periodic inspections of all production equipment.

21 CFR 820.70(g)(2) states: "Each manufacturer shall conduct periodic inspections in accordance with established procedures to ensure adherence to applicable equipment maintenance schedules. The inspections, including the date and individual(s) conducting the inspections, shall be documented."

An important thing for devicemakers to keep in mind when developing and implementing these procedures is that they must define and document their own goals, as well as explaining step-by-step what is to be done and who is to do it. There should also be a method of follow-up to ensure that the procedures are actually followed.

Excerpted from the *FDAnews* management report: *Three Phases of QSR-Compliant Equipment Control*.

Out-of-Calibration Equipment Plagues Contract Manufacturer

Not only was equipment found to be out of calibration at All Quality & Services' Fremont, California facility, but the contract manufacturer failed to document remedial actions, CAPA activities or investigate complaints, a January to February FDA inspection found.

The five-item Form 483 said that multimeters used to measure voltage of printed circuit boards (PCBs) and components were not calibrated.

Voltage testing for PCBs is one of the final quality control tests performed on the boards before assembly into a finished device for shipment.

During a walkthrough, the inspector observed that the facility lacked identification and calibration information for its multimeters.

"We asked the VP of Operation for the calibration records; however, he stated there were no records and the multimeters had not been calibrated," according to the 483.

The firm makes laboratory devices and surgical equipment including orthopedic surgical aids, image-guided catheter systems and image generators.

The FDA also found that the firm failed to document corrective and preventive and it failed to open a CAPA after being notified by a third party audit that the multimeters used to measure the voltage of the main board were not calibrated.

Four CAPAs that were reviewed were closed before the effectiveness of the corrective actions could be verified.

The agency also cited the contract manufacturer for not documenting personnel training or acceptance activities.

Read the All Quality & Services Form 483 here: www.fdanews.com/05-22-18-allqualityandservicesinc483.pdf.

483, *from Page 6*

The facility also lacked written MDR procedures and procedures were not adequately established to control product that did not conform to specified requirements. None of the non-conforming delivery or non-conforming material reports reviewed included documentation of an investigation or evaluation of whether an investigation was necessary, the agency said.

Rework and reevaluation activities were also not documented in the device history record, and CAPA procedures were inadequate.

The firm also failed to establish procedures for design changes or for evaluating suppliers or contractors, or to ensure sampling methods were adequate for their intended use.

Read the Medegen Medical Products Form 483 here: www.fdanews.com/05-22-18-medegenmedicalproductsllc483.pdf.

Abbott Diabetes Care Dinged for Inadequate Complaint Procedures

The FDA cited Abbott Diabetes Care for inadequate complaint evaluation procedures following a November to December 2017 inspection of its Alameda, Calif., facility.

The one-item Form 483 said the firm's complaint handling process for the FreeStyle Libre Pro Flash glucose monitoring system didn't provide adequate instructions for investigating medical device complaints to determine whether the device failed to meet specifications and the relationship of the device to the reported adverse event.

The 483 noted that the firm received a complaint that a patient developed an infection while using the FreeStyle Libre Pro glucose monitoring system, and the firm submitted an MDR for the adverse event, but the firm's investigation didn't include a review of the device history record or a testing of retained product.

The FDA said further investigation could include:

- Inspection and product testing, in an attempt to repeat the reported failure mode of product returned for investigation, to determine if the product meets specification;
- Review of the device history record for the device or its lot;
- Review of the tracking and trending data, including the frequency of the reported complaint; and
- Testing of retained product.

Read the Abbott FDA Form 483 here: www.fdanews.com/05-22-18-abbottdiabetescareinc483.pdf.

APPROVALS

FDA Clears MC10's Biometric Data Collection System

The FDA granted 510(k) clearance to MC10's BioStamp nPoint system, a platform used for healthcare data collection.

The system can continuously collect physiological data in home or traditional healthcare settings. It is designed to be used in clinical trials and research studies, and includes a rechargeable body-conforming sensor. It can measure vital signs, sleep metrics, general activity and postural classifications.

Casmed's OEM Version of Tissue Oximeter Cleared by FDA

The FDA approved Casmed's original equipment manufacturer version of its Fore-Sight Elite tissue oximeter.

The device displays tissue oximetry values through a Fore-Sight technology cable connected to sensors on the patient's forehead. It is designed for minimal user-interface modifications for use with third party monitors.

StimGuard Approved For Sacral Nerve Stimulator

StimGuard's wireless neuromodulation device received a CE Mark for treating chronic, persistent symptoms of overactive bladder.

The device injects a therapy using a needle and can be configured using an Apple iPad for advanced programming. It eliminates the need for implantation of a battery source in the patient, which requires surgery.

The nerve stimulator places a small device equipped with electrode contacts and an embedded chip in the patient's body through a needle paired with a wire receiver.

Additive Orthopedics Announces FDA Clearance of 3D Printed Bone Segments

Additive Orthopedics received 510(k) clearance for its patient-specific 3D printed bone segments, used to address internal bone fixation in the ankle and foot.

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

Approvals, *from Page 7*

The printed bone segments are used in certain cases of limb salvage, trauma and implant revision when there are few clinically available devices to address the patient's condition.

The segments use a lattice structure to promote bone-in growth instead of older, more open types of structures that use biologics for osteosynthesis.

Embotrap II Cleared For Treating Ischemic Strokes

The FDA granted marketing clearance to Cerenovus' Embotrap II for treatment of ischemic stroke, a mechanical thrombectomy device designed to retrieve blood clots from the brain.

The 510(k) application included results from the ARISE II trial of 228 patients at 11 U.S. and 8 European sites. The study found that physicians successfully restored blood flow in 80.2 percent of patients within 3 passes and in 51.5 percent of patients within a single pass.

The stent retriever can be used up to eight hours after the patient experiences stroke symptom onset and patients ineligible for IV tissue plasminogen activator therapy are candidates for treatment.

Motus GI's Pure-Vu System Receives Chinese Patent

The Chinese Patent Office awarded Motus GI a patent for its Pure-Vu System for cleaning the colon during colonoscopy procedures to improve visualization.

The device integrates with standard colonoscopes to enable cleaning during the procedure while preserving standard procedural workflow and techniques.

The system previously received 510(k) clearance from the FDA and CE Mark approval in Europe. It is currently being introduced on a pilot basis in the U.S. market. The company is planning to initiate a broader commercial launch in the U.S. and select international markets in 2019.

Xtant Cleared for Cervical Interbody System

The FDA gave Xtant 510(k) marketing clearance for its InTice-C porous titanium cervical interbody system, a scaffold material used for implant fixation.

The material is used as a bioactive scaffold and is cleared for use alongside Xtant's proprietary allograft lines, including the company's OsteoSponge, cortical fibers and viable cell allograft products.

InTice-C gives cervical intervertebral body fusion options for differing patient anatomies and comes in multiple footprint, height and endplate options.

Flow Cytometry-Based Test For HPV Receives CE Mark

IncellDx received a CE Mark for its HPV OncoTect 3Dx flow cytometry assay for human papillomavirus. The assay enables women to go beyond cervical cancer screening tests in determining if they are infected with a high-risk strain of HPV.

The test provides results in four hours, including the quantification of oncogene mRNA overexpression, proliferation and abnormal numbers of chromosomes.

The assay enables the identification of ectocervical cells and quantifies the percentage of cells that overexpress E6 and E7 mRNA.

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FDANEWS

EU MDR Compliance: *A Checklist for Meeting Manufacturing, Safety and Performance Requirements*

The new EU Medical Device Regulation is massive… complex… and confusing… and you must be ready to comply by May 26, 2020.

When the European Union revised its system of rules for medical device manufacturers in 2017, it replaced a longstanding set of directives on specific topics with one large document that covers all aspects of making devices in EU countries.

Not only did they consolidate all the rules, they gave them greater weight. Previously, medical device directives provided guidance but did not have the force of law. The new MDR, however, contains mandates that are legally enforceable by EU member countries.

The FDAnews report **EU MDR Compliance** can help. Our editors have combed through the regulations, picking out the most minute compliance points and building them into a checklist of 200+ requirements you can use to confirm that you are satisfying all the EU mandates for device manufacturing. The report provides:

- Definitions of key terms in the EU MDR
- Knowing where to find specific requirements in the 150+ page regulation
- Checklists that walk you through every aspect of manufacturing, safety and performance requirements
- A training tool for employees new to the regulations

EU MDR Compliance: *A Checklist for Meeting Manufacturing, Safety and Performance Requirements* is the tool that collects all the requirements, explains them and itemized them in an easy-to-use form to ensure compliance.

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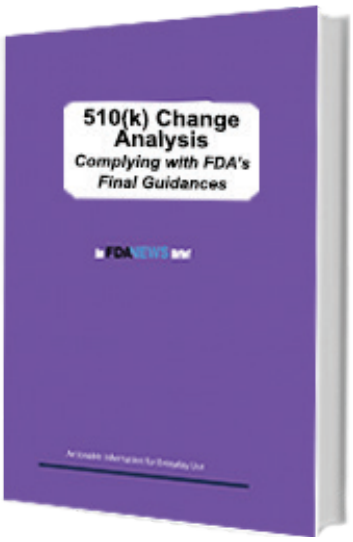

510(k) Change Analysis: *Complying with FDA's Final Guidances*

510(k) Change Analysis: *Complying with FDA's Final Guidances* breaks down the guidances finalized in October, 2017 — *Deciding When to Submit a 510(k) for a Change to an Existing Device* and *Deciding When to Submit a 510(k) for a Software Change to an Existing Device* — and provides a step-by-step method for making the right call for submitting a new 510(k) application. Expert-developed spreadsheets walk you through the questions you must ask and lead you to the proper conclusion.

After reading this book, you'll understand:

- What kinds of changes trigger the need for a new 510(k) application and which don't
- How to evaluate the effect of the change on the device's safety and effectiveness
- How to assess the risk the change may introduce
- The components of risk as described in ISO 14971
- How to follow the complex flowcharts the guidances present
- How to develop a risk matrix
- How to document the decision-making process, including justifying a decision not to file a new 510(k)

In addition to the decision-making spreadsheets that all but do the work for you, the report includes copies of both guidances and an example of a change analysis effort.

Order your copy of the **510(k) Change Analysis** brief for step-by-step instruction on deciding whether you need to submit a new 510(k) if you change an existing device.

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