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IN THIS ISSUE

EC Releases Guidelines On Benefit-Risk Analysis for Phthalates

The European Commission released final guidelines for devicemakers, notified bodies and regulators on how to perform a benefit-risk analysis for phthalates in medical devices.

The guidelines also describe how to evaluate possible alternatives for phthalates used in devices, including alternative materials, designs or medical treatments.

Widely used in plastics and polymers in a variety of applications for medical devices, phthalates such as Di-2-ethlyhexyl phthalate (DEHP) may be released from the plastic product into the human body. In addition to the impact on patients, the analysis should evaluate the risk for professional users exposed to the substance, the commission says.

The guidelines on the presence in devices of phthalates that are carcinogenic, mutagenic, toxic to reproduction (CMR) or endocrine

(See **Guidelines***, Page 2)*

MHRA Will Require 'UK Responsible Person' for All Devices, IVDs

Non-UK device and in vitro diagnostic makers will have to register their products with a "UK responsible person" if the UK crashes out of the EU without a deal, the Medicines and Healthcare products Regulatory Agency (MHRA) said in a new guidance.

Much like an EU authorized representative under the EU's Medical Device Regulation, devicemakers outside the UK must designate a "UK responsible person" with a UK-registered address.

The UK responsible person must ensure that the declaration of conformity and technical documentation have been drawn up and that an appropriate conformity assessment procedure has been carried out by the manufacturer, the agency says. The responsible person will keep a copy of the technical documentation and the declaration of conformity for inspection.

(See **MHRA***, Page 2)*

Guidelines, *from Page 1*

disrupting (ED) were developed by the EC's Scientific Committee on Health, Environmental and Emerging Risks.

The EU's Medical Device Regulation allows the use of CMR 1A/1B and endocrine disrupting substances above a concentration of 0.1 percent when a justification can be provided.

Phthalates classified as reproductive toxicants category IB are identified as substances of very high concern and are listed in Annex 5 of the guidelines.

When more than one CMR/ED is used simultaneously in a device, a justification should be provided for each of the phthalates and their combination, the guideline said, noting that some risk assessment data regarding the combination of phthalates are available since the European Food Safety Authority has released guidance on this.

The guidelines describe how to evaluate possible alternatives for phthalates used in devices, including alternative materials, designs or medical treatments. It said the risk associated with alternatives should be weighed against the use of CMR 1A/1B and ED identified phthalates covered under Annex I.

However, the risk is not the only parameter to consider. The impact of the possible alternatives on the functionality, performance and the overall benefit-risk ratio of the device should be evaluated, the commission says. The guidelines include a suggested risk analysis map.

Read the guidelines here: www.fdanews.com/09-26-19-Guidelines.pdf.

MHRA, *from Page 1*

The responsible person will serve as the go-between, forwarding to the manufacturer any requests by the Secretary of State for samples, or access to a device and ensuring that the Secretary of State receives the samples or has been given access to the device.

The measures include cooperating with the Secretary of State on any preventive or corrective action taken to eliminate or mitigate risks posed by devices. The responsible person will "immediately inform the manufacturer about complaints and reports from healthcare professionals, patients and users about suspected incidents related to a device for which they have been designated," the agency says.

In addition, the UK responsible person is required to "terminate the legal relationship with the manufacturer if the manufacturer acts contrary to its obligations" under the regulations and inform the Secretary of State and the relevant notified body.

Ireland Seeks to Mitigate Shortages

In related news, Ireland's Health Products Regulatory Authority (HPRA) asked device manufacturers to ensure sufficient stock levels and continuity of supply leading up to the Oct. 31 Brexit deadline and post Brexit.

The agency urged devicemakers to consider stocks in the supply chain and ensure arrangements are in place to allow for replenishment of stock, including allowing for potential delays.

The agency also outlined steps companies need to take to transfer certificates from a UK notified body to an EU notified body and to relocate UK-based European authorized representatives within the EU.

Read the MHRA guidance here: www.fdanews.com/09-27-19-MHRAnotice.pdf.

Read the HPRA notice here: www.fdanews.com/09-27-19-HPRAnotice.pdf.

FDA's Top Ten GMP Citations for FY 2019

An *FDAnews* analysis of the FDA's Form 483 inspection reports for fiscal year 2019 shows devicemakers continue to be tripped up at the same old hurdles.

According to agency inspection data logged between Oct. 1, 2018 and Sept. 17, 2019, the agency issued just 730 483s — 236 fewer than in fiscal 2018. But the top ten citations written up this year were largely in line with previous years.

The top citation was failure to establish CAPA procedures, which the agency flagged 283 times.

In second place were failures to establish procedures for receiving, reviewing and evaluating complaints by a formally designated unit, which appeared 215 times.

Purchasing controls (procedures for ensuring that all purchased or otherwise received products and services meet their specific requirements) not being properly established were the third most frequent citations in FY 2019, appearing 135 times.

A lack of written medical device reporting (MDR) procedures, or MDRs not being developed, maintained or implemented were the fourth most cited violation. They were written up 119 times this fiscal year.

In fifth place came slipups on process validations. Inadequate validations of processes "whose results cannot be fully verified by subsequent inspection and test" showed up 107 times.

Sixth was a lack of adequate procedures to deal with nonconforming products, while seventh was a failure to properly establish quality audit procedures (which ranked eighth last year); these were flagged 95 and 81 times, respectively.

CAPAs and/or results not being adequately documented came in eighth and occurred 59 times, moving down a spot from FY 2018.Failure to establish design control procedures ranked ninth with 52 occurrences.

Inadequate procedures for design changes came in at number ten, having been cited 48 times according to the data. Violations of device master records not being properly maintained were flagged only 37 times this fiscal year, compared with 63 times in 2018. — James Miessler

Top FDA Device GMP Inspection Findings for FY2019

1	Procedures for corrective and preventive action have not been [adequately] established.
2	Procedures for receiving, reviewing, and evaluating complaints by a formally designated unit have not been [adequately] established.
3	Procedures to ensure that all purchased or otherwise received product and services conform to specified requirements have not been [adequately] established.
4	Written MDR procedures have not been [developed] [maintained] [implemented].
5	A process whose results cannot be fully verified by subsequent inspection and test has not been [adequately] validated according to established procedures.
6	Procedures have not been [adequately] established to control product that does not conform to specified requirements.
7	Procedures for quality audits have not been [adequately] established.
8	Corrective and preventive action activities and/or results have not been [adequately] documented.
9	Procedures for design control have not been established.
10	Procedures for design change have not been [adequately] established.

Source: FDA

FDA Clarifies Agency Policy On Digital Health Tools

The FDA laid out its latest thinking on digital health tools in a package of six guidances released last week, highlighting the continued need for innovation.

Part of the agency's implementation of its Digital Health Innovation Plan, the documents include one revised draft, one final guidance and updates to four previously released final guidances.

"Our aim is to provide more clarity on our risk-based approach to digital health products, and, in particular, to provide more detail on those technologies and applications that would no longer be classified as a medical device," said FDA's Principal Deputy Commissioner Amy Abernethy.

The revised draft guidance advises on clinical decision support (CDS) software designed to help providers identify the best treatment plan for a patient's disease or condition. The revision clarifies the agency's oversight of such software products, based on public comments on a 2017 draft.

The agency's final guidance explains changes to medical software policies as a result of a regulatory amendment that removed certain software functions from the definition of medical devices. Mobile apps that only encourage a healthy lifestyle, for example, are generally not under the eye of the FDA, as they pose a low risk.

The updates to the four already-released final guidances bring them in line with current regulations. They address medical device data systems, image storage devices and communications devices, device software functions and mobile medical apps, policies for low-risk devices, and the use of off-the-shelf software in devices.

Read the revised draft guidance here: www.fdanews.com/09-26-19-SupportSoftware.pdf.

Read the final guidance here: www.fdanews.com/09-26-19-ChangesSoftware.pdf.

Read the updated final guidances here: www.fdanews.com/09-26-19-Guidances.pdf.

— James Miessler

FDA Promises Details On Electronic Submission Formats

Under the FDA's MDUFA IV commitments, the agency is developing electronic submission templates for device sponsors, but it says it's "not feasible to describe and implement the electronic formats that would apply to all submissions in a single guidance," in a draft guidance released last week.

Electronic submissions will be required for 510(k) premarket notifications, De Novo designations, premarket approval applications, product development protocols, humanitarian device exemptions, emergency use authorizations, and certain investigational new drug and biologics license application. The agency plans to issue separate draft guidances to specify formats for different types of submissions. Once finalized they will be binding, the agency says.

Read the draft guidance here: www.fdanews.com/09-27-19-eSubmissionParentGuidance.pdf.

483 Roundup: FDA Flags Three Firms for GMP Failures

The FDA cited devicemakers in Sweden, Germany and China for GMP and other lapses, including inadequate design history files and complaint handling.

ScandiDos: Inadequate design transfer procedures and lax documentation were among the problems uncovered at devicemaker ScandiDos during an FDA inspection at the firm's Uppsala, Sweden facility.

The company develops the Delta4 family of products, a treatment dose verification system. A 2018 release of the Delta Phantom, Delta SW and common firmware was distributed without the signatures for all listed participants, which conflicts with the firm's standard operating procedures, the Form 483 said.

The FDA said the firm's procedures don't adequately address the documentation, evaluation, segregation and disposition of non-conforming material, because there was no documentation for acceptance or rejection of incoming product.

In addition, device history records were not properly maintained. The FDA investigator said a review of device history records for the Delta4 Phantom between July 2016 to July 2018 found that at least 11 DHRs didn't include the dates of manufacture, the primary identification label, and the unique device identifier attached to the device.

The DHRs didn't include or refer to the location of acceptance records that demonstrated the device was manufactured in accordance with the device master record, the FDA said.

Rapid Biomedical: FDA investigators found sloppy medical device reporting procedures and a lack of software validation during an inspection of Rapid Biomedical's manufacturing plant in Bayern, Germany.

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

Complaint Classifications

Establishing a classification system for complaints helps organize your analysis. The customer is complaining the device is deficient in meeting one or more essential design output areas including: identity; quality; durability; reliability; safety; effectiveness; and performance.

If you are going to use this classification method, make sure your complaint SOPs clearly define each type and staff are trained to make decisions based on those definitions.

Ultimately, the devicemaker must make a key decision about each complaint: Does the complaint allege a serious incident — one that might have led or might lead to a death, a serious deterioration of someone's state of health or a threat to public health?

If the answer is yes, the complaint must be reported to the FDA or other regulator based on their regulations. If the complaint is determined to be "nonserious," it does not need to be reported but it must be recorded, investigated and classified for analysis purposes.

It's the way you use the results of this analysis that regulators emphasize. They want to know that you are tracking and identifying any significant increase in frequency or severity or other outlier uncovered in complaints and that you are using that information to make continual improvements.

Effective complaint management is a complex undertaking, involving staffing, training, data storage, trend analysis, reporting, information sharing, and meeting federal and international quality standards.

Complaint management involves all levels of a devicemaker's business: manufacturing, research, customer service, sales, field service, quality assurance, regulatory affairs, all the way up to the executive suites where the big decisions are made.

Excerpted from the FDAnews management report: *Complaint Management for Devicemakers — From Receiving and Investigating to Analyzing Trends*.

483s, *from Page 5*

The facility's MDR procedures didn't include a system for timely identification, communication and evaluation of events that may be subject to MDR requirements, the agency said in a Form 483 report.

In addition, software used in the firm's production and quality system was not validated and documented. The facility had used the software since 2005 for manufacturing, creating device history records, traceability and other quality management activities.

Rapid Biomedical's sampling plan for incoming quality inspections was not based on a sound statistical rationale, because random sample sizes were chosen, the FDA said.

Modern Medical Equipment Manufacturing: Poor stability studies, inadequate complaint records and failure to document design inputs and outputs were among the quality system failures discovered during an FDA inspection of Modern Medical Equipment Manufacturing's Guangdong, China facility.

The agency's investigators found that stability studies covering a disposable general electrode didn't cover all environmental conditions listed in the product labeling and didn't provide a justification for not verifying the functionality of the device for the full range of conditions listed on the label. For example, testing records didn't include humidity conditions, the agency said.

The company also failed to investigate a customer complaint about a malfunctioning device that came in contact with a patient's face and "generated burn risks," the Form 483 said, noting that the company didn't follow up with the patient to determine if a medical device report should be submitted to the agency.

Corrective and preventive action records were also found to be inadequate in that CAPAs opened during an FDA inspection in July 2018 were not addressed.

In addition, simulation testing conducted during design validation of the disposable electrode was not conducted on porcine kidney and liver as reported to the FDA in the 510(k) submission, the FDA said.

Read the ScandiDos Form 483 here: www.fdanews.com/09-27-19-scandiDosabd483.pdf.

Read the Rapid Biomedical Form 483 here: www.fdanews.com/09-27-19-rapidbiomedicalgmbh483.pdf.

Read the Modern Medical Equipment Manufacturing 483 here: www.fdanews.com/09-27-19-modernmedicalequipmanultd483.pdf.

'Patient Advisors' Can Expedite Device Trials, FDA Says

The FDA recommends using "patient advisors" to help improve medical device clinical trials, in a newly released draft guidance.

Because medical device trials include many endpoints as well as eligibility criteria that exclude some study participants living with the disease from participating in the trials, trials often take too long, cost too much for sponsors, increase burden for patients, and are delayed in providing beneficial medical technologies, the agency says.

"Patient advisors have experience living with a disease or condition and can be an advisor to improve the clinical investigation design and conduct, but they are not participating in the clinical investigation themselves," said acting FDA Commissioner Ned Sharpless in a comment on the draft.

The draft guidance stems from the FDA's Patient Engagement Advisory Committee meetings launched in 2017, at which the agency was urged to clarify how patient advisors can engage in clinical investigations.

Companies can work with patient advisors to improve informed consent, follow-up visits, endpoints and patient reported outcomes. Input from patient advisors will also reduce protocol violations and revisions, and streamline data collection, resulting in better quality data, the agency says.

Read the draft guidance here: www.fdanews.com/09-26-19-PatientEngagement.pdf.

FDA Explains New Safer Technologies Program

The FDA is introducing a new, voluntary program for certain medical devices and device-led combination products that are expected to significantly improve the safety of treatments for a disease or condition deemed less serious than those eligible for the breakthrough devices program.

Modeled on the breakthrough device program, the safer technologies program is expected to expedite development, assessment and review of these devices, the agency says. Devices and device-led combination products are eligible for this program if they are subject to review under a premarket approval application, de novo classification request, or 510(k).

The safer technologies program, or STeP, includes two phases. In the first phase, sponsors must request inclusion in STeP through a Q-submission. The second phase includes the prioritized review of subsequent regulatory submissions. The program is similar to the breakthrough device program in that it aims for timely communication, review team support and prioritized reviews, the agency says.

Read the agency's draft guidance on safer technologies here: www.fdanews.com/09-26-19-SaferTechsProgramGuidance.pdf.

FDA Unveils Framework for Safety, Performance-Based Pathway

The FDA has set out a framework how devicemakers will be able to demonstrate products are as safe and effective as a predicate device under an expansion of the agency's abbreviated 510(k) pathway for certain, well understood device types.

The agency is soliciting feedback from industry on identifying performance criteria and testing methodologies for devices within four class II device types: spinal plating systems, cutaneous electrodes for recording purposes, conventional Foley catheters, and orthopedic non-spinal metallic bone screws and washers.

The safety and performance-based pathway is appropriate when FDA has determined that:

- The new device has indications for use and technological characteristics that don't raise different questions of safety and effectiveness than the identified predicate;
- The performance criteria align with the performance of one or more legally marketed devices of the same type as the new device; and
- The new device meets all the FDA-identified performance criteria.

Devicemakers will still need to identify a predicate device for certain aspects of substantial equivalence, but instead of conducting direct comparison testing, they will be able to use the safety and performance-based pathway.

Read the agency's notice here: www.fdanews.com/09-26-19-Framework.pdf.

FDA Pilots Accreditation Scheme For Conformity Assessment

The FDA is establishing a pilot accreditation scheme for conformity assessment (ASCA) whereby testing laboratories may be accredited by accreditation bodies to assess the conformance of a device within certain FDA-recognized standards.

The agency is proposing to accept in-house testing laboratories as participants in the ASCA pilot.

An accredited testing lab may conduct testing to determine conformance of a device with at least one of the standards eligible for inclusion in the ASCA pilot.

A manufacturer that uses an ASCA-accredited testing lab can include a declaration of conformity with supplemental documentation as part of a premarket submission to the FDA. ASCA pilot participants include accreditation bodies, testing laboratories, device manufacturers, and FDA staff.

Read the ASCA guidance document here: www.fdanews.com/09-26-19-ASCAPilotGuidance.pdf.

APPROVALS

Abiomed Nabs Premarket Approval for Latest Heart Pump

The FDA granted Abiomed premarket approval for the Impella 5.5 with SmartAssist, its newest heart pump for treating cardiogenic shock.

The minimally invasive device can be used by heart surgeons for up to two weeks in the treatment of cardiogenic shock that occurs less than 48 hours after open heart surgery or acute myocardial infarction.

The temporary pump can deliver flows greater than six liters per minute at its peak and is easier to insert than the previous model. The device eliminates the need for sternotomies or removal of tissue.

ProciseDxs Near-Patient Diagnostic Platform Gains CE Mark

In vitro diagnostics firm ProciseDx has earned the CE Mark for its point of care rapid diagnostic test platform.

The test quantifies diagnostic and treatment monitoring markers for inflammatory and autoimmune diseases, including celiac, and metabolic syndromes such as diabetes and pre-diabetes. It is slated to be launched in Europe next year, the company said.

Personal Genome's Tissue Complete Assay Gets CE Marked

Personal Genome Diagnostics has gained the CE Mark for another PGDx elio panel, this time for its tissue complete assay.

The panel tests for somatic alterations across 507 genes. It can detect single nucleotide variants, small insertion/deletions, amplifications and rearrangements.

The tissue complete assay also tests for microsatellite instability (MSI) and tumor mutation burden (TMB). MSI has received FDA approval for identifying cancer patients whose tumors may respond to immune checkpoint inhibitor therapy and the use of TMB for that purpose is at the clinical trial stage.

Exact Sciences' Colorectal Cancer Test Gets Expanded Indication

The FDA approved Exact Sciences' noninvasive colorectal cancer screening test, Cologuard, for eligible patients aged 45 years and older.

Cologuard is a stool DNA-based colorectal cancer screening test for average-risk individuals. The test uses a biomarker panel, which analyzes a stool sample for 10 DNA markers.

FDA Approves Roche's Donated Blood Screener

The FDA granted approval to Roche's individual blood donation screening test for use on its cobas 6800/8800 systems.

Roche's cobas Babesia test is a whole blood test used to screen donations. The company said it follows agency guidance that advises screening and testing for Babesia to reduce the parasite's transmission from infusions.

The diagnostic test detects parasites that live in red blood cells. This is significant because the parasite can't be detected in traditional plasma or serum samples, Roche said.

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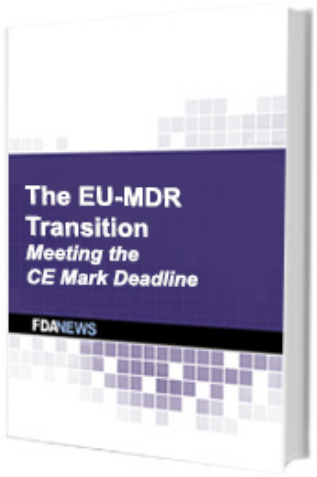

The EU-MDR Transition: *Meeting the CE Mark Deadline*

If you plan to continue putting devices on the European market, you'll need to implement the EU-MDR.

Due to the slow progress in the EU companies are being guided through a soft transition plan.

Dan O'Leary — industry expert with more than 30 years of experience in quality, operations and program management — explains the hybrid system, where you maintain a device certificate under the MDD and a QMS under the MDR.

The EU-MDR Transition: *Meeting the CE Mark Deadline* explains how to take advantage of the soft transition to the new regulation. The soft transition allows companies to retain certain aspects of the current CE Mark applications while following new registration requirements, if their notified bodies approve.

But, what does that really mean?

This report breaks down all the rules and explains all the implications of a soft transition, providing a path to follow to full compliance:

- **Transition Timeline:** All the dates and deadlines on the transition timeline
- **SOPs:** How to develop an SOP for the post market surveillance you will have to conduct under EU-MDR
- **Adverse Events:** How to report adverse events
- **Forms:** What new forms will be required
- **Technical documentation:** How to structure technical documentation for your hybrid system

Start implementing the hybrid MDD/MDR system to keep your products on the European market until the full EU-MDR comes into effect.

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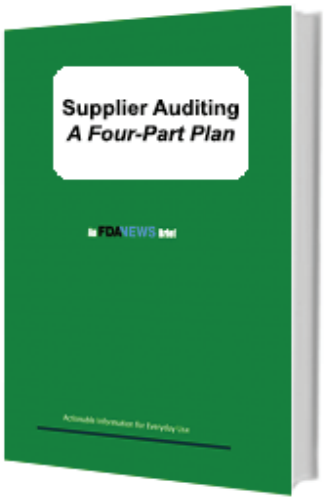

Supplier Auditing: *A Four-Part Plan*

You deal with hundreds of suppliers.

And you need to make sure each and every one of them meet your quality standards.

How can you keep your eye on that many suppliers?

You need a supplier auditing program that helps you stay on top of all your outsourced operations. The FDAnews Brief **Supplier Auditing: *A Four-Part Plan*** helps you build a system that shows the FDA and other regulators that you hold the reins when it comes to supplier quality:

- Decide who to audit. Start with risk assessment. Not every supplier needs a comprehensive annual audit. Some present bigger potential problems than others and should be monitored frequently. Others may be trusted long-standing contractors that you check up on only every few years. How can you know which is which?
- Decide what to audit. Do you need to examine a supplier's entire quality system, or just a particular process or procedure?
- Decide when and how to audit. What steps will you take and what questions need to be answered? Create a checklist to keep the audit on track.
- Keep up with your suppliers. Maintain a file on each supplier — a dossier, if you will — and develop a list of those you have given your stamp of approval. Having these records on hand will be invaluable when FDA investigators start looking at your supplier management system.

Get your supplier audit program in shape now with **Supplier Auditing: *A Four-Part Plan*.**

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