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IN THIS ISSUE

FDA to Begin ORA Reorganization in Mid-May

After nearly four years of discussion and expectation, the FDA will begin its inspection reorganization in mid-May.

Beginning May 15, the current five-region structure will be replaced with six program areas, covering medical devices and radiological health; pharmaceutical quality; biological products; bioresearch monitoring; human and animal food; tobacco and a program for import operations.

"Program alignment is to establish these more vertical commodity-specific programs so you just have a device inspector, that is all they do—and that will allow them to better focus and have the right expertise and training," CDRH Director Jeff Shuren told a House hearing on medical device user fees. "That will start to drive more consistency and more timeliness in the conduct of inspections."

The Office of Regulatory Affairs will keep its 20 existing districts. District directors will keep their responsibilities, but will also specialize in one program as division directors, the FDA said. The FDA has no plans to close offices or relocate personnel.

Gottlieb to Recuse Himself from Agency Decisions on More than 20 Companies

FDA Commissioner nominee Scott Gottlieb will recuse himself for one year from decisions relating to more than 20 companies, including large device makers, according to his ethics disclosure form.

Gottlieb, whose nomination hearing is scheduled for April 5, plans to resign from 13 industry roles upon being confirmed and will divest his company stock and other financial interests.

Gottlieb plans to resign from board positions at GlaxoSmithKline and Daiichi Sankyo, and will also recuse himself from dealings concerning Bristol-Myers Squibb, for a one-year period following participation in a consulting project. He had previously resigned from positions at Tivorsan Pharmaceuticals, Gradalis and Strike Bio, but will still recuse himself for the next year.

(See **Gottlieb***, Page 2)*

CDRH Priorities Focus On Data, Quality

The FDA's device center has tripled the number of staff with quality credentials to conduct on-site quality training and inspections.

The center had aimed to boost staff by 10 percent, but it ended up with a 300 percent increase, according to a report.

One of CDRH's top priorities is the National Evaluation System for Medical Devices (NEST), which gathers real-world evidence to support regulatory decision making.

The agency has acknowledged that some data may lack rigor compared to data collected in clinical trial settings, but said it may help support approval decisions. CDRH expects to release final guidance on this issue in 2017.

CDRH had set a goal of collecting data from 25 million patient records by the end of 2016, but reported it actually gained access to more than 28.6 million patient records via clinical registries, claims data and electronic health records. To gather the evidence, the FDA struck deals with 14 device registries earlier this year (*IDDM*, Jan. 9).

The Case for Quality initiative is another top priority for the center. Launched in 2011, the initiative aims to elevate the focus of medical device stakeholders from baseline regulatory compliance to sustained, predictive practices that advance medical device quality and safety to achieve better patient outcomes. As part of the Case for Quality initiative, the agency partnered with the Medical Device Innovation Consortium (MDIC) and the Capability Maturity Model Institute to develop a voluntary third party program using quality metrics to assess quality.

The partners are working with three device manufacturers to develop a proof-of-concept voluntary pilot program that will report back in 2017.

Read the CDRH Strategic Priorities document here: www.fdanews.com/03-31-17-StrategicPriorities.pdf.

Gottlieb, *from Page 1*

He will also resign from jobs at the venture capital firm New Enterprise Associates, as well as at T.R. Winston & Co., a banking firm.

Gottlieb previously served as the FDA's deputy commissioner for medical and scientific affairs from 2005 to 2007.

Gottlieb's financial connections with pharmaceutical companies could cause speedbumps during his Senate confirmation process — as they did Tom Price's nomination for HHS secretary earlier this year, which focused on Price's stock purchases. Indeed, the February 2016 confirmation of Robert Califf to the post was briefly held up, partly over his ties to pharmaceutical companies.

Gottlieb's ethics disclosure statement can be found here: www.fdanews.com/03-29-17-GottliebEthicsLetter.pdf. — Conor Hale

Shuren Tells Congress FDA Workload Continues to Rise

CDRH Director Jeff Shuren told a house panel that the FDA's workload continues to increase about10 percent every year, in part because of efforts to approve more innovative medical devices and make better use of real-world evidence in post market surveillance.

The agency still needs all of the money called for by the latest medical devices user fee agreement (MDUFA IV) even if regulations and staffing are cut under the Trump administration, he testified before the House Energy and Commerce Committee.

MDUFA IV would aim to collect $183 million in fiscal 2018, increasing annually to $213 million through fiscal 2022. The fees were previously negotiated by the FDA and regulated industry, to cover medical product reviews through fiscal 2022 (*IDDM*, March 27).

Robert Kieval, founder and chief development officer of CVRx and member of the Medical Device Manufacturers Association's board of directors, noted that MDUFA IV calls for FDA auditors to cite the specific justification and applicable regulation for any deficiency letter or data request.

"It's frustrating to us when we receive requests for data or deficiency letters that are unreasonable, without reason, or aren't germane to the evaluation of a product's safety or efficacy," he said. The new agreement "will ensure that queries are meaningful and that time spent by both parties is productive."

Diane Wurzburger, executive of regulatory affairs for GE Healthcare, testified on behalf of the Medical Imaging & Technology Alliance (MITA). She said the new user fee agreement will facilitate the FDA's pre-submission program, under which the agency can provide feedback on a device before the manufacturer submits an application.

MDUFVA IV also establishes the Accreditation Scheme for Conformity Assessment (ASCA) program, which allows for devices to be evaluated according to specific recognized consensus standards by certified testing laboratories. "MITA is a strong proponent of the use of voluntary consensus standards and believes that the ASCA program will reduce time to decision and provide more predictability to the process," she said.

AdvaMed President and CEO Scott Whitaker said the latest user fee package "lays the groundwork for further FDA performance improvements," and that delayed congressional approval "could jeopardize the opportunity to improve the efficiency and predictability of FDA's review process for medical technology, which would negatively impact our industry's ability to bring innovative diagnostics, treatments, and cures to patients."

Materials from the hearing are available here: www.fdanews.com/03-29-17-hearingmaterials.pdf.

FDA Reports to Congress On Regulatory Science Achievements

In a regulatory science update to Congress, the FDA cited its successes in helping to improve nonclinical evaluation of medical devices and develop new diagnostic tests for use during disease outbreaks.

CDRH researchers developed computational tools to support nonclinical evaluation of medical products, including mathematical representations of the human body that can be used to predict the effects of medical devices.

CDRH supported the regulatory public health response to the Ebola and Zika viruses by helping to develop diagnostic tests and other tools, along with producing reference materials and science-based guidance.

The agency also cited the Centers of Excellence in Regulatory Science and Innovation – located at the University of Maryland, Georgetown University and the Johns Hopkins University — including joint efforts between the University of California at San Francisco and

(See **Science**, *Page 4)*

UK's MHRA Releases New Guidance On 'Virtual Manufacturing'

Beginning Sept. 1, companies that put their names on devices made by other companies must have their quality management systems (QMS) audited and full technical documentation reviewed by notified bodies, says new guidance from the UK's MHRA.

Previously, notified bodies accepted summaries of technical documentation from "virtual manufacturers" and did not require full QMS audits. However, under new Medicines & Healthcare products Regulatory Agency (MHRA) guidance, a company that outsources the design and manufacture of a device must keep the full technical documentation available and submit to audits if the product is marketed under the company's name.

Technical documentation must show that a marketed device meets regulation requirements. It also must be fully integrated into a firm's QMS and contain all relevant data pertaining to labels, instructions for use, and risk assessments.

If a virtual manufacturer does not hold the rights to a product's design, it may provide a technical file with redacted proprietary information. However, the OEM must agree to fully disclose all technical information directly to the appropriate notified body, as well as submit to unannounced audits, post-market surveillance, and other requirements.

Read the guidance here: www.fdanews.com/03-29-17-virtualmanufacturers.pdf.

Science, *from Page 3*

Stanford University, as well as between Yale University and the Mayo Clinic. The centers aim to address gaps in regulatory science.

In the period covered by the report, the FDA developed laboratory capabilities to monitor continuous manufacturing with advanced process control systems, and led the creation of a 3-D printing facility, to more closely analyze quality and performance issues in devices, drugs and combination products developed through 3-D printing technology.

The FDA also made several organization changes over the past two years to address regulatory science issues. For example, it piloted a Regulatory Science Research Program Review to help CDRH reviewers and bench scientists collaborate more effectively.

Read the full progress report here: www.fdanews.com/03-30-17-FDAReport.pdf.
— Zack Budryk and Jeff Kinney

PEOPLE ON THE MOVE

Biostage has promoted **Saverio La Francesca, M.D.** to president. Dr. La Francesca has served as Chief Medical Officer of the Company since April 2014. Prior to joining Biostage, Dr. La Francesca served in the department of cardiovascular surgery and transplantation at the DeBakey Heart and Vascular Center at the Houston Methodist Hospital.

Acuamark Diagnostics has recruited **Dr. Michael Hanbury** to its board of directors. Currently, Dr. Hanbury is a healthcare advisor for the Pritzker Group and is on a number of medical device company boards. Formerly, he was VP, laboratory operations and laboratory excellence for Quest Diagnostics, and Ppresident and chief operating officer at Solstas Lab Partners.

LightIntegra board has dubbed **Bill Dubiel** as president and CEO. He joins LightIntegra from Personal Genome Diagnostics, where he has been the chief commercial officer. He has held senior level positions at CyVek, Ventana, Roche, Bayer and Chiron Diagnostics.

Therachon has hired **Dr. Maarten Kraan, Ph.D., M.D.**, chief medical officer. Most recently, Dr. Kraan was senior vice president, head of innovative medicines respiratory and inflammation at AstraZeneca. Prior to that, Dr. Kraan was vice president, head of clinical research and experimental development inflammation at Hoffman – La Roche. Before that, Dr. Kraan was vice president, immunosciences at Bristol Myers Squibb.

New EU MDR Presents Major Compliance Hurdles

The European Union's new Medical Device Regulation (MDR) will create significant compliance headaches for manufacturers — including new harmonized standards, classification rules, and conformity assessment procedures.

ISO 13485 and every other harmonized standard will need to be revised to conform to the MDR, Dan O'Leary, president of Ombu Enterprises, told attendees March 29 at the Medical Device Quality Congress, sponsored by FDAnews.

Ensuring that devices adhere to the new standards will be time-consuming and expensive in many cases, O'Leary said.

Some devices will have to be reclassified under the MDR's new classification rules. There are four device classifications (I, IIa, IIb, and III) and four groups of classification rules encompassing non-invasive devices, invasive devices, active devices, and a catch-all category of special rules.

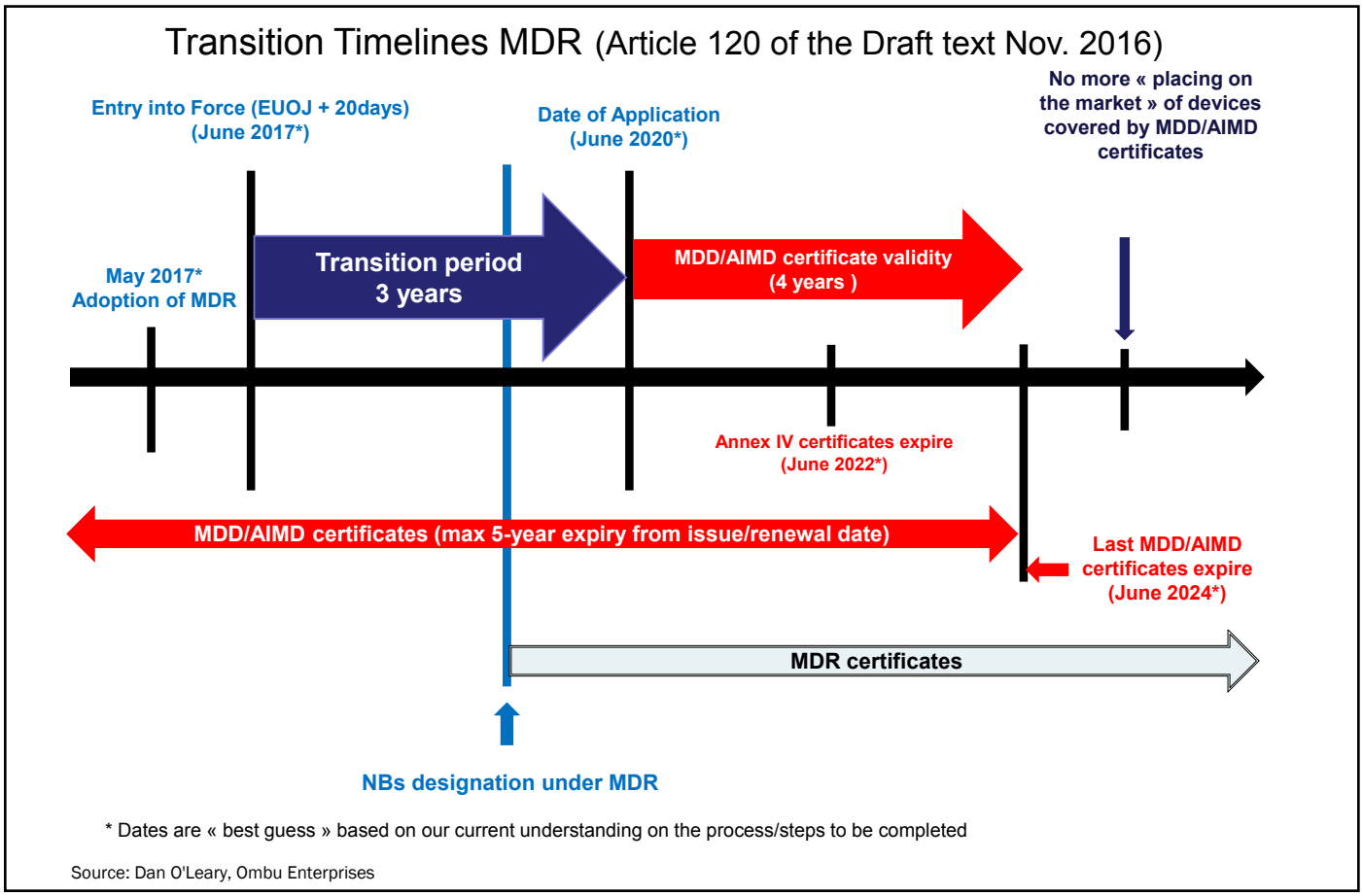
Each device class has more than one conformity assessment pathway. There are specific requirements for Class III implantable and Class IIb implantable devices, as well as separate requirements for Class I sterile devices, reusable surgical instruments, and devices that have a measuring function.

All told, classification and conformity assessment will be a "huge amount of work," O'Leary said. To get ready for compliance, he said, manufacturers should:

- Determine the class under the new rules for each of their existing devices;
- Determine the possible conformity assessment paths; and
- Develop the information needed to satisfy the elements in the selected conformity assessment path.

The MDR also requires manufacturers to designate at least one individual who ensures regulatory compliance. This person is responsible for checking

(See **MDR**, *Page 6)*



Proposal Would Combine FDA Regs For IVDs, Lab-Developed Tests

A legislative discussion draft being floated in Congress would require the FDA to develop one set of regulations governing both in vitro diagnostics (IVDs) and laboratory-developed tests (LDTs) — to create a more predictable and timely path to market.

Currently, the FDA regulates IVDs but does not actively regulate LDTs. The Diagnostic Accuracy and Innovation Act, which is circulating as a discussion draft, would create a new category of products called in vitro clinical tests (IVCTs) that comprised both IVDs and LDTs and would be regulated separately from devices, drugs, and biologics.

The discussion draft would establish FDA jurisdiction over IVCT development and manufacturing while maintaining Centers for Medicare and Medicaid Services' (CMS) oversight of laboratory operations. It also would establish a regulatory structure for IVCTs that addresses risk classification, premarket requirements, modifications, quality, post-market monitoring, and innovation.

Cosponsors Reps. Larry Bucshon (R-Ind.) and Diana DeGette (D-Colo.) are inviting comments on the draft by April 7. They plan to formally introduce the measure after reviewing the comments, a spokesman for Bucshon told *IDDM*.

They say the proposal would bring "much needed certainty" to the diagnostic industry by applying the same regulatory principles to the same activity regardless of where a test is developed.

In January, instead of finalizing draft LDT guidance, the FDA released a discussion paper outlining a possible approach that would focus on new and significantly modified high- and moderate-risk LDT (*IDDM*, Jan. 16). The agency is expected to release two final guidances and one draft guidance related to in vitro diagnostics this year (*IDDM*, Jan. 2).

Read the discussion draft here: www.fdanews.com/03-27-17-discussiondraft.pdf.

MDR, *from Page 5*

device conformity before release, updating technical documentation and declarations of conformity, and seeing that the company meets post-market surveillance and reporting requirements.

Large and medium-sized companies should have at least two employees designated as responsible individuals. Small companies, as defined in the MDR, can get by with a single contractor or consultant.

Although there is a three-year transition period after the MDR is adopted and before it comes into force (see chart), in practice this period will only be about one year because of time needed for the redesignation process.

The MDR and in vitro regulations took another step toward final approval March 7 when they were adopted by the European Council. The final step in the EU's adoption process is a vote by the European Parliament, which is expected in April (*IDDM*, March 13).

Form 483 Round Up: FDA Flags Four Device Facilities

The FDA has cited four device firms for a range of compliance issues including inadequate test methods, production controls, and CAPA procedures.

In an inspection at Fujifilm's Carrollton, Texas, facility in January, inspectors observed that the accuracy and reproducibility of the facility's test methods were not established or documented. The facility was manufacturing 70 percent isopropyl alcohol USP using invalidated methods without appropriate testing. For example, gas chromatography tests were not validated to ensure accuracy.

In addition, batch production and control records did not document the accomplishment of each significant step in manufacturing, processing, packing, and holding, according to the Form 483. For example, batch records failed to include complete traceability of all components used in manufacturing 70 percent isopropyl alcohol USP.

Life Science Outsourcing: During a June 2016 inspection of Life Science Outsourcing's Brea, Calif., facility, inspectors found that procedures for identifying, investigating, correcting, and implementing corrective actions had not been implemented. For example, the company initiated four CAPA reports pertaining to mislabeled products. The CAPAs were closed as effective but failed to identify the cause or correct the mislabeling. Life Science continued to receive customer complaints regarding labeling issues.

The Form 483 also said certain processes were not validated. These included a cleaning step conducted during manufacturing, and a visual inspection method used to inspect finished products — including sterile surgical and implantable products — for particulate matter.

The facility did not have proper complaint review procedures were not established, including a procedure requiring investigation to identify the root cause of complaints and implement corrective actions. For example, the wrong label was printed for a particular lot of products, and the problem was missed during inspection. Life Science failed to identify the cause, and the complaint was closed after personnel were retrained without taking any other action to prevent recurrence.

Glatt: The FDA hit Glatt Air Techniques with a Form 483, citing failure to sanitize utensils or quarantine drug products.

In a January inspection of the devicemaker's Parsippany, New Jersey, facility, FDA officials determined the company did not clean or sanitize equipment and utensils properly, citing "rust-like material and darkish-brown material" on washing machine surfaces. An "extensive amount" of off-white powder was found on the inside surface of a dryer lid, according to the Form 483, and because Glatt also failed to keep logbooks for the affected equipment, inspectors could not verify its usage history.

The facility did not conduct continued cleaning process verification for the equipment used for high-volume commercial products, according to the 483, and manufactured numerous products over a two-year period without verification studies for the cleaning procedures. Inspectors also found numerous containers of products produced by the company within the warehouse with a status indicator as well as a "deficient" quarantine.

Ascent Consumer Products: Ascent Consumer Products drew a Form 483 over problems with reporting, testing and complaint responses.

In a November 2016 inspection of Ascent's Melville, New York, facility, FDA officials found the company did not prepare required reports on device safety and effectiveness. Ascent failed to conduct or request evaluation of a novel product used for nasal irrigation, according to inspectors.

The agency also faulted Ascent for failing to conduct scientific studies demonstrating the effectiveness of its filter units, or to establish procedures for identifying products during all stages of production and distribution.

The firms did not respond to requests for comment.

Read the Form 483s here: www.fdanews.com/03-31-17-4Form483s.pdf.

BRIEFS

Zoll Wins Health Canada Clearance for Two AEDS

Massachusetts-based Zoll has received marketing clearance from Health Canada for its AED 3 and AED 3 BLS automated external defibrillators.

The AED 3 BLS model is designed specifically for first responders. The model includes a CPR dashboard, which shows critical information such as the rate and depth of each compression. It is also Wi-Fi enabled so first responders can export clinical data.

The units are not available for sale in the United States.

Mirabilis Medical Wins CE Mark for Uterine Fibroids

Mirabilis Medical has been granted a CE Mark to market a robotically assisted, non-invasive ultrasound system to treat uterine fibroids.

The clearance was granted based on the completion of an initial clinical trial, which treated 73 women in Mexico with an average active treatment time of less than 10 minutes.

The company has also been cleared by the FDA to conduct a pivotal study in the U.S., which will start in the second half of this year. A total of 180 patients will participate in the trial at 12 sites, including nine in the U.S., two in Canada, and one in Germany.

FDA Approves iCAD's PowerLook Tomo Detection Device

New Hampshire–based iCAD has received FDA premarket approval for its PowerLook Tomo detection platform.

The 3D image improves detection of hidden or obscured areas on a 2D mammography. The platform also identifies suspicious areas that radiologists may not see initially.

The device received a CE Mark and Health Canada approval in 2016.

Syneron Candela Wins CE Mark for CO2RE Intima

Syneron Candela has secured a CE mark for CO2RE Intima, a non-surgical in-office laser treatment that relieves the effects of childbirth and aging on the vagina.

In a clinical study, 82 percent of women showed a statistically significant improvement after treatment.

FDA Grants Investigational Device Exemption For Human Trial of Prosthetic Hand

The FDA awarded an investigational device exemption to Florida International University for a human trial of its neural-enabled prosthetic hand system.

The device is not approved by the FDA for U.S. commercial distribution.

FDA Clears Providence Medical Technology's Cervical Cage-L System and Facet Screws

Providence Medical Technology has won two FDA marketing clearances for its Cavux cervical cage-l system and Ally facet screws to compliment the company's DTRAX Spinal System for use in cervical fusion.

The Cavux cervical cage-l system is made from titanium and is available in a variety of sizes.

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

Editor: Jeff Kinney +1 (703) 538-7634 jkinney@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: Cynthia Jessup, Conor Hale, Zack Budryk **Managing Editor:** Declan Conroy **President:** Cynthia Carter

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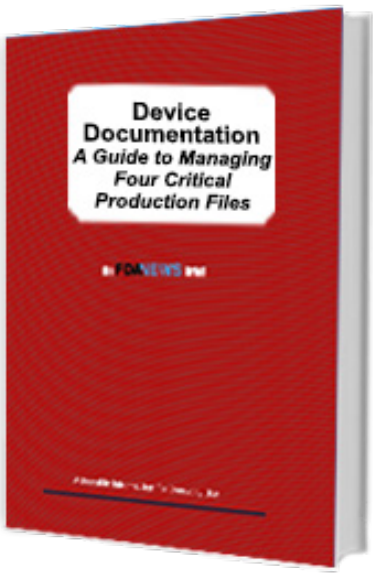

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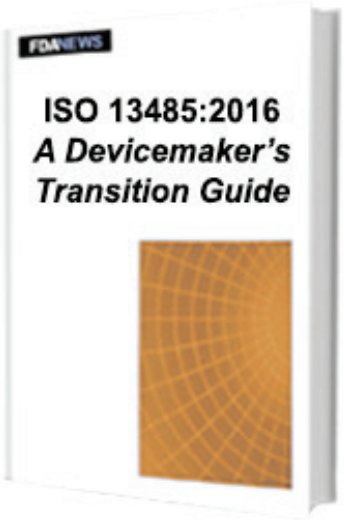

ISO 13485:2016
A Devicemaker's Transition Guide

The ISO 13485 have rules changed — and you need to know how.

Our team of experts have spent hours parsing out every clause in the new version of the rules and compared them to ISO 13485:2003.

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