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IN THIS ISSUE

FDA to Expand High Performance Computing to Boost Clinical Trial Efficiency

The FDA plans to expand its capabilities in high performance computing to help build disease models and simulate device clinical trials as part of an agency initiative announced Friday by Commissioner Scott Gottlieb.

The project will focus on modernizing the agency's regulatory processes and reducing the time, cost and uncertainty of bringing a product to market.

Today, CDRH is building in silico regulatory models for product design and evaluation, including the development of a digital library of models and a family of virtual patients for device testing, Gottlieb said.

Streamlining development and regulatory barriers can ultimately lower the cost of the product, he said.

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

Australia's TGA Releases New Guidance On Conformity Assessment Procedures

Australia's Therapeutic Goods Administration released new draft guidance spelling out what steps are needed when devicemakers that have been issued conformity assessment certificates in Australia and want to make a change.

The guidance includes events that trigger a transfer of a conformity assessment certificate and associated manufacturer responsibilities. It is one of three the TGA will release related to new conformity assessment procedures in the Australian Regulatory Guidelines for Medical Devices (ARGMD). Australia's device regulations are undergoing a major update, and more guidance will be issued on a range of other issues including notified bodies in Australia, accelerated reviews for devices and other procedural changes.

For any device changes, manufacturer s are expected to have written procedures in their quality management systems that cover change

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

Guidance, *from Page 1*

management and guides to decision making. They must consider the impact of any changes on regulatory requirements and risk management and must document the risks and decisions.

Critical changes would include a change in a sterilization method or manufacturing process, a change in the location of a key step in manufacturing such as outsourcing. Other changes that require notification include changes to the product range, changes to product design, changes to labeling and instructions for use.

Changes that are not considered substantial would include:

- Changes to non-critical parts or suppliers that still meet the acceptance criteria established by the manufacturer;
- Changes to manufacturing equipment or processes that are not likely to influence the level of risk; and
- Changes to the packaging or labeling that do not alter compliance.

Companies must notify the TGA of any substantial change before supplying affected products affect. When a conformity assessment certificate will be transferred, the TGA should be notified within three months. Events that trigger a transfer would include bankruptcy, a name change, disposal of the business or amalgamation with another company.

The TGA will soon release a new online conformity assessment application form and will launch a new certificate repository that will automatically generate conformity assessment certificates when an assessment is concluded.

Included in the TGA guidance is a checklist for devicemakers that covers essential principles for medical devices. The 20-page checklist is comprised of 15 sections, including: design and construction and intended use; safety and adverse events; verification and validation and risk control elements related to substances used in manufacturing; infection and microbial contamination; protection against radiation; implantable devices and IVDs.

The regulator also noted that annual fees will now apply to IVDs, and companies will be charged AUS$660 (U.S. $500) for each entry for the 2017 to 2018 financial year.

Read the guidance here: www.fdanews.com/07-05-17-Australia.pdf.

Gottlieb, *from Page 1*

The FDA also released its finalized work plan for spending the $500 million authorized by the 21st Century Cures Act over the next decade.

The plan, submitted to Congress in early June, largely follows the draft considered by the FDA's Science Board in May (*IDDM*, May 12). With $40 million set for fiscal 2017, dollar amounts for fiscal 2018 and beyond will need to be appropriated annually by Congress.

Since the Cures Act was passed in December, CDRH has exempted more than 70 Class I device types from 510(k) submission requirements. The center has proposed exempting another 1,000 Class II device types based on an initial determination that premarket review is not necessary.

CDRH also amended its current regulations to allow more devices to qualify for a humanitarian device exemption for small patient populations, and will allow researchers to seek approval for device clinical trials through a central institutional review board rather than mandating the use of local review boards.

In addition, new requirements for reusable device types take effect Aug. 8 — the FDA will require validated instructions for use and data regarding cleaning, disinfection, and sterilization in 510(k) submissions.

The FDA also established a Cures Act steering committee, which compiled a list of all agency-related requirements and deliverables, with deadlines for guidances and public meetings.

The FDA's work plan is available here: www.fdanews.com/07-07-17-CuresWorkPlan.pdf.

The agency's list of deliverables is available here: www.fdanews.com/07-07-17-21CuresDeliverables.pdf. — Conor Hale

Regulatory Expert Gert Bos Shares Insights on Europe's Notified Bodies

Devicemakers are closely watching the EMA and the U.K.'s Medicines and Healthcare products Regulatory Agency for assurances on how conformity assessments will unfold under the new EU regulations. With fewer notified bodies in the EU, and the added complication of Brexit, the next steps remain uncertain. Qserve Group Executive Director Gert Bos — an auditor and former head of a notified body — spoke with IDDM on the changing environment and how devicemakers can plan for upcoming conformity assessments.

Question: *How is the U.K. planning on handling notified bodies with respect to the U.K.'s exit from the European Union?*

Answer: There are several contributors to this debate, and multiple strategies are being considered. Besides the possibility that the Brexit process will be reversed and all things stay as normal, there are a number of possible scenarios to consider, such as:

- Brexit combined with a direct or indirect mutual recognition agreement (MRA) via the European Free Trade agreement: the U.K. would continue to use the EU CE-marking process and U.K. notified bodies would remain in place;
- Brexit, followed by direct or indirect MRA: As there would be a gap in U.K. continuing to use the EU CE-marking process, U.K. notified bodies might temporarily be unable to perform their tasks; debate would be needed on whether notification can be re-instated when an MRA is signed, or if new designation is to be in place;
- Brexit without MRA: U.K. notified bodies would no longer be operational for EU CE marking, but might get a role in market approval and oversight for a new U.K. medical device legislative framework.

The MHRA publicly indicated it is planning for a smooth process in which both MHRA and U.K. notified bodies may continue their current role. Meanwhile, U.K. notified bodies are indicating they are preparing for alternative solutions to continue serving their CE-certificate holders, such as by applying as a notified body in another country, or by extending the scope of their EU-based notified bodies.

When a new notified body is in place, transfer of certificates might be proposed to the certification holders. As certificate holders would already be confronted with labeling changes due to the notified body number changing, some are indicating to presume this would be an administrative transfer, rather than a transfer with acceptance review. As current interpretation on MDD compliance requirements is rapidly evolving, transfer reviews might find a compliance backlog, and hence transfers might become complex. A pragmatic approach will be required to ensure a smooth process.

Q: *How should devicemakers wanting to market their products in the U.K. approach notified bodies?*

A: The key is good communication with a U.K. notified body if you are working with them. Get in touch, get to understand their strategy and expected timelines, discuss transfer processes where needed, and apply so you're not last in line! Also, remember that U.K. notified bodies did not push for such an agenda; this was a decision from the voters in U.K..

Q: *How do you see the role of EU notified bodies changing?*

A: Key elements in the new role include focus on full compliance instead of looking for sufficient evidence on conformity. Secondly, in the transfer to the EU Medical Device Regulation (MDR) and Invitro Diagnostic Device Regulation (IVDR), there will not be any harmonized standard in the early days, so the conformity assessment cannot use the presumption of conformity via use of standards as is widely practiced.

(See **Q&A***, Page 4)*

Dutch Regulators to Adopt FDA's UDI Device-Labeling System

The Dutch medical device authority has reached a voluntary agreement with industry on the use of UDI codes for medical devices, using FDA's UDI system as a template.

The Dutch Minister of Health signed the agreement in late June with healthcare providers and device distributors and manufacturers. Under the agreement, Dutch hospitals will exclusively use the UDI system to identify and trace medical devices, making the Netherlands the first European Union member state to agree to the system.

Data requirements for Dutch signatories will be the same as under the FDA's system. Going forward, however, Dutch regulators may amend the requirements to better conform with the UDI regulations other EU nations develop. — Zack Budryk

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Q&A, *from Page 3*

Hence, the focus is on demonstrating full compliance to the legal requirements directly. Enhanced supervision on notified bodies will continue, but most notably several consultation and scrutiny processes have been added, and notified bodies will find it harder to disagree with the various agencies recommendations. The essence of the notified body work will not change, but the reality might well find more black and white strict interpretations.

Q: *How should devicemakers view the looming exit of the U.K.? Should they be concerned?*

A: I'd rather use the word vigilant. With that I mean that manufacturers should proactively approach their notified bodies to communicate details of the transition planning in various outcomes of the Brexit negotiations. Details from such communication can then feed into their corporate risk management assessments. Most difficult in this regard is the timeline associated with the Brexit process. This ends around 14 months before the end of the three-year MDR transition, just at the time when first designations under the MDR are expected.

This means that transferring to a new notified body, which might well be the sister organization of the current notified body, most likely will need to happen before the MDR designation is in place, so under MDD/AIMD or IVD designation, but in a time where MDR implementation is already partially ongoing. It will be essential to get MDD/AIMD/IVD certification in place early, as they will form the basis for the soft-transition market continuation. At such a time, labeling, marketing, declaration of conformity, free sales certificate, global registrations based on CE marking, etc., will need to be updated, and they will again need to be updated once MDR certification is in place.

Besides the uncertainty over which process needs to be followed, depending on the course of the Brexit negotiations, more resources will be required for all the double administrative handling.

Former FDA Deputy Chief Says More Surveillance is Badly Needed

Despite a pressing need in the device sector for postmarketing surveillance, studies remain infrequent and limited in scope, and though the FDA has envisioned a robust system using medical records to track device safety, any such system is years from adoption, would need additional funding, and may not survive the new administration's interest in deregulation.

That's according to Joshua Sharfstein — who served as FDA deputy commissioner from 2009 to 2011, was then secretary of the Maryland state Department of Health and Mental Hygiene, and is now associate dean at the Johns Hopkins Bloomberg School of Public Health.

To illustrate the point, Sharfstein and researchers Rita Redberg and Alison Jacoby use power morcellators as an example, in a Journal of the American Medical Association article.

Morcellators

The laparoscopic surgical devices that allow minimally invasive hysterectomy and myomectomy for large uteri and fibroids, were first described in 1993 and were then widely adopted by gynecologists. Uptake of the new technology was rapid. From 2005 to 2013, the rate of outpatient laparoscopic hysterectomy increased from 31.4 to 161.6 per 100,000 adult women, whereas the rate of inpatient hysterectomy declined from 172.1 to 72.1 per 100,000 adult women, with doctors using power morcellators for an estimated 55,000 to 75,000 procedures annually in the United States at peak, wrote Sharfstein et al.

In 2013, however, power morcellation came under scrutiny when a highly publicized case raised awareness that some masses diagnosed as fibroids might actually be undiagnosed cancers — and the use of the devices might spread malignant cells from these tissues throughout the abdomen. The FDA investigated the issue, and, in April 2014, issued a safety communication estimating the risk of an unexpected uterine sarcoma at 1 in 350 patients undergoing hysterectomy or myomectomy.

Later that year, the agency required a "black box" warning label on power morcellator devices. After that, the use of power morcellators saw a steep drop, with the largest manufacturer of the devices withdrawing them from the market.

Much controversy ensued. Many charged that the FDA failed to act sufficiently to protect patients, saying the agency should have removed the devices from the market. Others claimed FDA acted too aggressively and interfered inappropriately with patient care. Some said women should have been able to choose the technology for their procedures if they wanted it and understood the risks.

Competing Views

"The dispute reveals, in part, that there remain competing views about how regulatory decisions should be made about the use of medical products as evidence emerges on safety risks," wrote Sharfstein et al. "But it also indicates how such ideological disagreements become more prominent when there is a lack of evidence on risks and benefits at the time of approval, coupled with a lack of ongoing data collection to address key questions."

Other information clouded the matter: The FDA estimated the risk of an unexpected uterine sarcoma at approximately 1 in 350 women undergoing hysterectomy or myomectomy, while others have estimated the risk at approximately 1 in 2000.

Which is correct and should be weighed more heavily?

"These and other empirical questions are unresolved in part because of what is missing: a comprehensive system of data collection based on the experience of many thousands of women who have undergone these procedures," wrote Sharfstein et al.

(See **Surveillance***, Page 6)*

Surveillance, *from Page 5*

Morcellators, like many devices cleared through the 510K pathway, entered the market based on their "substantial equivalence" to prior devices; in this case, the equivalence was to a device used in arthroscopic joint surgery.

Even though the risk of potentially spreading cancer was known at the time of FDA clearance of the first of these devices in 1991, no clinical studies to assess the issue were required and no postmarketing requirements for data collection were put into place, wrote Sharfstein et al.

"Without such requirements, there was little incentive for the industry sponsors of the device to voluntarily gather such data," the researchers wrote.

"Moreover, physicians did not demand this information, instead relying on individual clinical experience. If the FDA had established a strong surveillance system, the agency could have reviewed outcomes years earlier, with far higher–quality data than are available today."

Sharfstein told *IDDM* that unfortunately, this cycle may need to be repeated a few more times before meaningful change will come.

"The FDA is clearly interested in better postmarket surveillance," he says. "It may take a few more controversies like this one to convince device makers and the clinical community of the value of this type of data."

Until a postmarketing surveillance approach for medical devices is established that can answer essential questions quickly, clinical medicine will remain in data purgatory, vulnerable to the next dispute over the safety of a new device or medical technology, wrote Sharfstein and his colleagues.

"Escaping this state requires recognizing that a common ground exists beyond ideological debates about regulatory decision making: strong data requirements that benefit patients, physicians, and industry alike," Sharfstein et al wrote.

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BRIEFS

MHRA Updates Recommendations For Metal-on-Metal Hip Replacements

The UK's Medicines and Healthcare products Regulatory Agency has updated its recommendations for metal-on-metal hip replacements because of concerns about the devices' safety and durability.

In August 2010, Johnson & Johnson subsidiary DePuy Synthes recalled two models of its hip replacement systems, while the National Health Service ended most metal-on-metal hip replacement procedures due to high failure rates.

In 2012, MHRA recommended annual blood tests and imaging for metal-on-metal hip replacements showing symptoms of tissue reactions and for all patients with larger or DePuy ASR implants. The new recommendations expand the annual screening to include all female patients who have had hip resurfacing and all male patients with smaller femoral head implants.

Novo Nordisk Recalls Cartridge Holders For Insulin Delivery Devices

Novo Nordisk recalled insulin cartridge holders used in some batches of its NovoPen Echo because they may crack or break if exposed to certain cleaning agents or chemicals. Using a device with a cracked or broken cartridge holder could result in the device delivering a lower dose of insulin which could potentially lead to high blood sugar, the company said.

Novo Nordisk received numerous complaints of damaged cartridge holders and some reports of adverse events. It said it has corrected the problem.

483 Roundup: FDA Cites Seven Firms for Procedural Issues

The FDA issued Form 483s to seven device facilities for a range of deviations including non-compliance with their SOPs and problems with complaints and equipment maintenance.

Oxford Performance Materials: The FDA cited Oxford Performance Materials for five issues from environmental control procedures to equipment maintenance.

The agency issued a Form 483 to Oxford's South Windsor, Conn., facility, following a March/April inspection. According to investigators, the facility did not conduct cleaning validation for the compound used to clean its HTR-PEKK cranial implant to ensure the compound's effectiveness. Investigators also observed a bag of the material used to finish the implants that was ripped and repaired with packing tape, and receiving records indicated acceptance of material without a record of inspection.

The facility also failed to established acceptance criteria for monitoring viable and non-viable samples, and its process validation for pre-vacuum steam sterilization for cranial implants did not include the review and approval of the report.

Biowave: The FDA cited Biowave for its quality audit procedures and management review.

The agency conducted an April inspection at the devicemaker's Norwalk, Conn., facility and found the company's had not established procedures for internal quality audits, a repeat observation.

Neurotron: The FDA issued a Form 483 to Neurotron over problems with its product instructions and failure to calibrate equipment.

In an April inspection of the devicemaker's Pasadena, Md., facility, inspectors noted the company's repair order instructions for its products did not provide adequate instruction and none of the 10 service reports reviewed documented who serviced the device or the test and inspection data.

The FDA also faulted the device manufacturer for its calibration procedures. The firm failed to follows its own SOPs on calibration.

TAG Medical Products: During a March inspection, investigators reviewed 14 complaints received by TAG Medical Products between November 2012 and March 2017 at its facility in Ha Zafon, Israel. Four of the complaints constituted adverse events according to TAG's description, but they were not documented as such or reported to the FDA, a March inspection found.

Direx Systems Corp.: Similarly, Direx Systems Corp. did not include required information in its service reports, according to the FDA. An April inspection of the company's Canton, Mass., facility found that while the firm's service procedures require documentation for all tests, the information was not included for several service records.

Avery Biomedical Devices: An April inspection of Avery Biomedical Devices' facility in Commack, NY found the firm did not comply with its clean room control procedures and lacked humidity or temperature monitoring devices in the clean room.

Transoject: A March inspection of Transoject's facility in Neumunster, Germany, found the firm failed to adequately assess whether a complaint qualified as a reportable adverse event.

Read the full Form 483s here: www.fdanews.com/07-07-17-Seven483s.pdf. — Zack Budryk

PEOPLE ON THE MOVE

Artificial heart manufacturer **CARMAT** has appointed **Wenzel Hurtak** as its new director of manufacturing. Hurtak was previously business director of new products for Contract Medical International and has also held positions with Johnson & Johnson and Integra LifeSciences.

Diagnostic testing device manufacturer **Qualigen** announced **Kurt H. Kruger** will join its board of directors effective June 26. Kruger has worked in medical technology for the past three decades and joined Qualigen after three years leading the life sciences banking arm at WR Hambrecht & Co.

India Classifies 462 Devices, 250 IVDs Under New Regs

India's Office of the Drug Controller General has classified 250 medical devices and 25 invitro diagnostics under new device regulations that become effective in January 2018.

India's device regulations separate devices from drugs for the first time. The new regulations classify devices into four risk-based categories — Class A to Class D — with Class D devices carrying the highest risk. The criteria by which devices are classified is specified in Rule 4, Chapter 11 of the new rules.

As the central authority, the DCGI enforces rules for importing and manufacturing higher-risk Class C and Class D devices. The DCGI also oversees clinical trials and inspections for devices in these classes. Of the newly classified devices, 84 devices fall under Class D, 157 fall under Class C, 198 are now under Class B, and 23 under Class A.

Newly classified devices that fall under Class D include a wide range of cardiac devices such as catheters, stents, valves, pacemakers and ventricular bypass devices. Also included in the list are implantable prostheses and stimulators, cerebrospinal devices, hemodialysis systems, radiofrequency ablation devices, percutaneous tissue ablation devices, fiber-optic catheters, CNS shunts, embolization devices, cerebrospinal catheters, cochlear and retinal implants.

Devices that fall under Class C include some prostheses such as esophageal, chin, ear, nose, ankle and elbow joints, injectable fillers and adhesive agents, stents for other organs including the esophagus, gallbladder, duodenum, colon and pancreas. Also included in Class C are penile implants, dental implants, bone grafting material, hearing aids, IUDs, tissue expanders and biopatches among others.

Examples of Class B devices include infusion pumps, endoscopes, angiography guide wires and angioscopes, vessel dilators, aspiration needles, cervical drains, rectal balloons, biopsy kits, tracheostomy trays, various cannulas, and a range of catheters.

Lower-risk Class A devices don't need to be licensed, but they do need to be audited by notified bodies to verify conformance with quality management standards.

New invitro diagnostic devices on the list include 11 Class D IVDs, 117 Class C IVDs, 119 in Class B and three IVDs in Class A.

Higher-risk Class D IVDs include those intended for blood grouping or tissue typing, including HIV test reagents and kits, syphilis test reagents, and malaria screening reagents and kits.

Examples of Class C IVDs on the list include reagents and kits for infectious diseases, anticoagulant monitoring, reagents for monitoring drug levels used for therapy or abuse, blood gas analysis and diabetes management tests.

The Central Drugs Standard Control Organization also noted that the agency will continue to streamline its procedures by modifying provisions of the Drugs and Cosmetics Rules 1945.

The CDSCO is accepting comments until July 31 on the streamlined procedures.

Read the CDSCO notice here: www.fdanews.com/07-05-17-India.pdf.

Canada to Require Acute Care Hospitals To Report Serious Device Incidents

New Canadian regulations would require certain healthcare providers to report serious medical device incidents to Health Canada.

The proposed amendment to the country's Food & Drugs Act would require full incident reports to Health Canada from any hospital that provides acute care products.

The agency proposes a 30-day reporting timeline for serious MDIs, with the clock starting when the institution first documents the event. Health Canada says this window achieves the necessary balance between a timely response and the time respondents will need to complete a thorough report.

Read the consultation paper here: www.fdanews.com/07-05-17-Canada.pdf. — Zack Budryk

APPROVALS

FDA Authorizes In Vitro Devices for Zika Detection

The FDA has issued two emergency use authorizations for in vitro diagnostic devices used to detect the Zika virus.

In February 2016, the HHS determined Zika presented significant potential for a public health emergency. In light of this, the FDA has issued emergency use authorizations for DiaSorin's Liaison XL Zika Capture IgM Assay and Nanobiosym Diagnostics' Gene-RADAR Zika Virus Test.

The agency also revoked its authorization for Roche's LightMix Zika rRT-PCR Test, at Roche's request.

FDA Clears Summit's Jaw Fracture Recovery Device for Marketing

Summit Medical's non-invasive jaw fracture recovery device secured FDA clearance for widespread marketing.

The device uses a system of sutures between the teeth to fix the jaw in place evenly for the recovery process. The use of sutures is more efficient and comfortable than wire-based devices, which can pose a safety threat to patients and surgeons. The device could also potentially be applied in clinical settings rather than operating rooms, reducing costs and delays.

Brazilian Regulator Approves Waters Corp's Spectrometry, UPLC Systems

Brazil's National Health Surveillance Agency (ANVISA) has approved Waters Corporations' mass spectrometry and UPLC systems for in-vitro diagnostic use.

The devices the approval makes available include the Acquity UPLC I-Class/Xevo TQD IVD System, the TQ-S micro IVD System and the TQ-S IVD System.

FDA Clears Cooling Cap For Solid Tumor Cancer Patients

The FDA cleared the expanded use of Dignitana's DigniCap Cooling System to reduce hair loss during chemotherapy for cancer patients with solid tumors.

The computer-controlled system is used during the chemotherapy treatment. The cap is worn on the head and circulates liquid to cool the scalp. A second cap made from neoprene holds the cooling cap in place and acts as insulation.

The cooling is intended to constrict blood vessels in the scalp, which reduces the amount of chemotherapy that reaches cells in the hair follicles. The cold temperature also decreases the activity of the hair follicles and slows down cell division, making them less affected by chemotherapy.

Edwards Lifesciences Gets FDA Nod for Inspiris Resilia Valve

The FDA has approved Edwards Lifesciences' Inspiris Resilia aortic valve.

The approval follows a pivotal trial in which two-year data from nearly 700 patients showed no indications of valve thrombosis, nonstructural valve dysfunction or structural valve deterioration.

The company expects to market the device on the U.S. early next year. It is already available in Europe and a launch is planned later this year in Japan.

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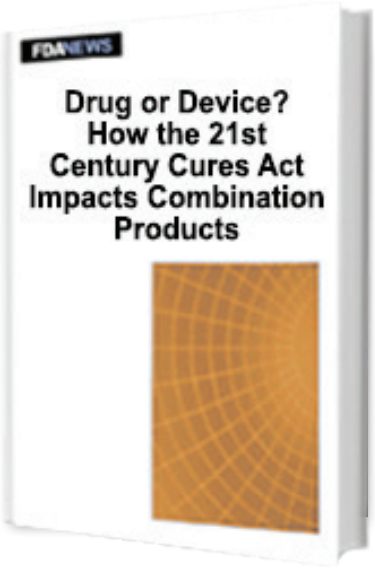

Drug or Device? How the 21st Century Cures Act Impacts Combination Products

Combination products remain one of the most difficult regulatory challenges for life sciences innovators.

Which FDA Center has the lead?

Will I need one marketing application or two?

Will I need a drug to be cross-labeled and approved for use with my device?

These and many more questions can make combination product sponsors feel like they are entering an unforgiving regulatory labyrinth.

The 21st Century Cures Act requires the FDA — over the next several years — to issue guidance that will create a structured process and best practices for managing the development and reviews of drug/device/biologic combinations. The law provides for a streamlined approach to GMP for combination products similar to what the agency has recently announced through rule and guidance.

Drug or Device? How the 21st Century Cures Act Impacts Combination Products takes a close look at the FDA's new authority governing combination products, as well as several new provisions under the 21st Century Cures Act that could usher in a new era of interdisciplinary product reviews at the FDA. You will learn:

- How the 21st Century Cures Act defines primary mode of action
- How to use pre-RFD (Request for Designation) meetings with the FDA to hammer out a customized review process that meets the sponsor's needs
- And more...

Order your copy of **Drug or Device? How the 21st Century Cures Act Impacts Combination Products** for practical advice on the newest changes in the law on combination products and a look around the corner at how sponsors of combination products should seek to position their products to ensure a least burdensome and optimal regulatory pathway.

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