INTERNATIONAL DEVICES & DIAGNOSTICS MONITOR

Vol. 5, No. 9
April 29, 2019

IN THIS ISSUE

FDA Urged to Clarify Voluntary Quality Standards for Combination Products

A trade group representing hybrid drug- and device-makers is urging the FDA to draw bright lines among the agency's centers as it considers voluntary quality standards.

The Combination Products Coalition (CPC), a Washington, DC-based trade association, is asking the FDA to clarify the scope of CDER's proposed voluntary quality guidelines, how it will integrate with standards laid out by CDRH and what types of standards it expects CDER to adopt.

In January, the agency issued a draft guidance that they hoped would allow CDER officials to "informally recognize" voluntary consensus standards related to pharmaceutical quality that are potentially useful to industry and CDER staff. The comment period closed Monday.

The coalition says it supports the principles behind the draft guidance but worries that the "relatively broad" wording may be confusing for companies that make combination products.

(See **Quality**, *Page 2)*

MedTech Europe Says EU MDR/IVDR Transition is Not Workable

MedTech Europe is warning European regulators that the EU's new regulatory system for devices won't be ready on time and said the delay will jeopardize patient lives.

"Our industry is prepared to submit product files to comply with the new Medical Device Regulation (MDR)," the lobbying group's CEO Serge Bernasconi said in an open letter to European regulators. "However, we cannot do so. The new regulatory system is not ready to function."

The EU has mandated that some 12 Notified Bodies will be designated by the year's end for assessing the conformity of devices under the MDR. assess the conformity of certain products before

(See **Transition**, *Page 2)*

Transition, *from Page 1*

being placed on the market. Bernasconi said the designation and capacity of notified bodies continues to be a critical concern, and only one notified body has been designated to the MDR.

The European Commission proposed to designate 12 different notified bodies to serve as clearinghouses for device approvals, a drastic reduction in the number of notified bodies previously. MedTech Europe says the reduced number of notified bodies will create a logjam of devices in the regulatory pipeline.

"A severe consequence of this is that European startups and SMEs, which represent 95 percent of the medical device industry, are already turning to the United States, China and other regions to develop and roll out their innovations and bring their related economic activity outside of Europe," Bernasconi said.

"This situation is clearly untenable," he said, "and time has run out to build a functioning regulatory system."

MedTech Europe said that recent attempts to provide relief through a grace period and warehousing only work for a portion of devices currently available and only partially achieve their objective.

Read the letter here: www.fdanews.com/04-26-19-MedTechEurope.pdf.

Quality, *from Page 1*

"To ensure transparency," the coalition "requests that FDA explicitly state in the draft guidance that the CDER program applies to the device constituents of combination products under CDER jurisdiction to ensure the continuation of such an approach."

The coalition would like the agency to "confirm which elements of the combination product fall within the scope of" the guidance, such as design and manufacture. Coalition members are also curious about how the proposed quality program will mesh with CDRH's Standards and Conformity Assessment Program for devices. "Currently, the applicability of the CDRH Program to such products is not explicitly clear."

Manufacturers of combination products would be okay with "applying the existing CDRH program to device constituents" of combination products but if regulators take this approach, "we also recommend clarifying which elements of the existing CDRH program may be applied to the devices constituent," CPC said.

The draft guidance repeatedly emphasizes that it's "informal" but makers of combination products makers "have to understand how FDA will respond to a development program that a sponsor has followed in good faith."

As to the standards involved in any CDER quality program, the coalition urges the regulators to decide whether they're thinking about targeted standards—such as those that apply to needle-based injection systems—or "vertical standards" such as those offered in guidances on risk management in medical devices.

The CDRH program includes vertical standards and the coalition finds them beneficial, allowing manufacturers to use "consensus-driven approaches across the organization in order to meet cGMP as well as individual product requirements."

Read the coalition's comments here: www.fdanews.com/04-15-19-CPCComment.pdf.
— Bill Myers

FDA Clarifies Labeling Identifier Rules for Convenience Kits

The FDA considers first aid and other "convenience" kits a single device for regulatory purposes, the agency said in final guidance.

The agency is hoping to simplify unique device identifier regulations for so-called convenience kits, which had required different labels for each of the unique devices in every kit.

Federal rules define "convenience kit" as "two or more different medical devices packaged together for the convenience of the user." The regulators now consider that definition "to mean a device that contains tow or more difference medical devices packaged together and intended to remain packaged together."

The guidance applies not just to first-aid kits, but to orthopedic device sets where each device is taken out of its package and placed in a sterilization tray and that include a limited number of implants for a given patient in a given surgery. It also includes single-use, disposable aid kits and kits with single-use and reusable devices.

Any kit with multiple devices should have production identifiers for each device in the kit, the agency says.

Read the guidance here: www.fdanews.com/04-25-19-FDAguidance.pdf.

FDA Addresses Safety Concerns For Surgical Staplers and Staples

The FDA issued a draft guidance and proposed order designed to ensure the safe and effective use of surgical staplers and staples for internal use, following concerns the agency identified in medical device reports.

Surgical staplers for internal use should be moved to a higher-risk category that scrutinizes them more intensely before they're cleared for marketing, the agency said.

The agency proposes reclassifying the products from low risk (Class I) to moderate risk (Class II) medical devices with special controls. The reclassification would let the agency require premarket review and establish special controls for the staplers, including obligatory performance testing and demonstration of usability. It would also allow for "specific labeling elements" to support safe use.

The devices are currently not required to submit a premarket notification to the FDA before marketing. The agency said the reclassification is needed "based on new information."

It also issued draft guidance containing recommendations for the labeling of surgical staplers and staples for internal use. The agency said it decided to address the labeling of the devices because of malfunctions and misuse that led to adverse events, including death.

The guidance recommends that manufacturers place visible contraindications on their products regarding their use on tissues for which stapling is overly risky, including a statement noting that the device shouldn't be used to staple necrotic, friable, ischemic or edematous tissues.

CDRH Director Jeffrey Shuren said the guidance will help devicemakers ensure their labeling provides adequate information on hazards, contraindications and other safety issues.

Read the draft guidance here: www.fdanews.com/04-26-19-staplersguidance.pdf.

Read the proposed order here: www.fdanews.com/04-26-19-surgicalstaplers.pdf.

— James Miessler

CDRH Offers Draft Guidance On Nitinol Medical Devices

CDRH has issued draft guidance for sponsors of devices containing nitinol that specifies what information should be included in their premarket submissions.

For devices manufactured with multiple types of nitinol, the FDA recommends providing information on each type of nitinol. The recommendations are based on the time period that the device would be in contact with the human body.

(See **Nitinol***, Page 4)*

Combination Products Get Extra Year for Postmarket Compliance

The FDA gave sponsors of combination drug/device products another year to get their IT affairs in order before complying with new postmarket safety reporting requirements.

Companies that make products that would have to report either to the drug or device reporting databases now have until July 2020 to comply with the agency's December 2016 final rule. Companies that make products related to vaccines have until January 2021.

Last year the agency published a final guidance on the new rule that requires companies that hold the rights to constituent parts of combination products—say, an insulin maker whose product was used in a pump—to file postmarket safety reports. The industry had asked the FDA to clarify the scope of the guidance.

The agency said it delayed enforcement of the rule so companies could build up the information technology infrastructure to comply with the new rules. On Tuesday, the agency extended the deadline even further.

The FDA expects companies to build up "robust IT systems and internal processes" to make sure they are tracking and reporting adverse events for combination products, an agency spokesman told *FDAnews*.

Read the FDA's extension notice here: www.fdanews.com/04-23-19-FDAguidance.pdf.
— Bill Myers

Nitinol, *from Page 3*

The performance behavior of nitinol depends on a number of factors, including alloy composition, thermal history and surface processing, and the FDA recommends including information on material composition, manufacturing parameters such as heat treatments and surface processing, whether the device is tuned to pseudoelasticity or shape memory behavior, and phase transformational temperatures of the finished form.

Other considerations include mechanical testing, corrosion resistance testing, biocompatibility, and computational stress and strain analyses.

Used in cardiovascular devices such as stents, heart valves, guidewires and vena cava filters, nitinol, an alloy of nickel and titanium, possesses shape memory behavior characteristics. Its use has increased in recent years due to its ability to return to its original shape after being deformed or after heat is applied. However, it requires special considerations compared to conventional metals due to its thermomechanical behavior and processing sensitivity.

In vivo corrosion of nitinol may decrease the device's safety profile or performance by adversely impacting mechanical properties and/or biocompatibility, the guidance says.

Read the guidance here: www.fdanews.com/04-26-19-NitinolTechnicalGuidance.pdf.

EU Device Group Releases Guidance On Eudamed Compliance

The EU's Medical Device Coordination Group has issued guidance on how devicemakers should register devices that do not have unique device identifiers (UDIs) with Eudamed, the EU's new medical device database.

The guidance describes legacy devices as those covered by a valid EU certificate that will continue to be placed on the market after the Medical Device Regulations (MDR) go into effect on May 26, 2020.

The new guidance notes that there are some inconsistencies in the timelines, largely because the database is still being developed and it may not be functional by the deadline. In addition, the MDR is not explicit in requiring that legacy devices are subject to UDI obligations.

Devicemakers will have until November 2021 to register with Eudamed. But if the system is not fully functional by that time, they will have until May 2022 to register.

However, the MDR device registration requirements mean the Basic UDI will be the access keys for device-related information in Eudamed. This means that registration of a device is normally possible in Eudamed only if a proper Basic UDI-DI is assigned to the device.

Legacy devices that will be registered in Eudamed will require two other unique access keys to replace the UDI keys, the guidance notes. For this purpose, a Eudamed DI (device identifier) will be assigned to the device instead of the Basic UDI-DI, and a Eudamed ID will be assigned instead of a UDI-DI.

It remains to be seen whether the Eudamed DI will be entirely generated by Eudamed or the device manufacturer. But the Eudamed ID will always be automatically generated by Eudamed.

"In case a legacy device has been already registered in Eudamed and that same device becomes at any point in time an MDR-compliance device, that MDR device should be considered as a new device requiring a new registration," the guidance document says.

It also points out that in the case of a serious incident or field safety corrective action, the incident must be reported immediately even if the device is not yet registered in the database.

The Eudamed system includes a public website for anonymous users to search and view publicly available data and a restricted website for database content management with access to all data an authorized user has the right to access.

Distributors and importers that assume the obligations of device manufacturers also assume responsibility for unique device identification labeling. This means that distributors and importers must apply for registration as manufacturers (*IDDM*, Oct. 26, 2018).

However, if the manufacturer is identified on the label rather than the distributor or importer, the manufacturer is responsible for meeting the UDI obligations under the quality system regulation.

Read the guidance on registering legacy devices here: www.fdanews.com/04-26-19-mdcg20194.pdf.

Read the timelines here: www.fdanews.com/04-26-19-mdcg20195.pdf.

FDA Finalizes Guidance For UHMWPE Orthopedic Devices

CDRH released final guidance for sponsors of orthopedic devices containing ultrahigh molecular weight polyethylene (UHMWPE) with advice on information to include in requests and submissions.

The guidance provides sponsors with recommendations for premarket notification submissions, de novo requests, premarket approval (PMA) applications, humanitarian device exemptions (HDEs) and investigational device exemptions (IDEs). The FDA says manufacturers who believe that certain information or testing recommended in the guidance does not apply to their device should "provide a rationale" explaining why.

Manufacturers are advised to include information on material processing, shelf-life,

(See **UHMWPE**, *Page 6)*

FDA Warns Boston's TEI Biosciences Over 'Systemic' Quality Failures

The FDA issued a warning letter to TEI Biosciences' for "systemic" quality failures the agency found during an Oct. 9 to Nov. 2, 2018, inspection of its Boston, Mass., facility.

The facility makes collagen-based medical devices used for wound care, soft tissue repair and reconstruction surgery, including the Xenform Soft Tissue Repair Matrix.

Although the firm took additional corrective and preventive actions following the inspection, the agency was not satisfied. For example, the facility lacked data to show that the water system used to manufacture devices was free of bacterial endotoxins.

In addition, the FDA said the manufacturing process for TEI's Xenform extracellular bovine matrix devices did not follow the firm's validation protocol.

Inspectors noted that data was lacking to demonstrate bacterial endotoxin testing of the EBM devices, and there were numerous discrepancies between the firm's current procedure and its quality control procedure.

The warning letter cites the firm for failing to test the medical devices with the largest surface area as "worst case" sampling for the bacterial endotoxin verification study. TEI revised instructions for running routine samples, the FDA said, but it lacked data to demonstrate that this step didn't affect the finished test results.

TEI failed to establish and maintain procedures to prevent contamination of equipment or product by substances that could have an adverse effect on product quality, the warning letter says.

Although the firm opened additional corrective and preventive actions following the FDA inspection and is in the process of correcting deficiencies, the agency said the deficiencies demonstrated a "systemic failure of your firm's quality systems."

During the inspection, the FDA investigator noted 16 non-conforming material reports related to tears found on pouches during the lyophilization process. According to the firm's CAPA procedures, if no tears were found during a certain period of time, the corrective action was verified as effective. However, the CAPA was closed even though six additional tears were identified.

Read the warning letter here: www.fdanews.com/04-25-19-TEIBiosciencesWL.pdf.
— James Miessler

UHMWPE, *from Page 5*

biocompatibility and the type of UHMWPE being used. Regardless of the type—conventional, highly crosslinked (HXLPE), antioxidant highly crosslinked (AO-HXLPE) or non-conventional — manufacturers should identify the starting resin, resin consolidation method and terminal sterilization method. Additional information, including mechanical and chemical characterizations, should be provided, though recommendations vary depending on the type of UHMWPE being used.

The guidance notes that UHMWPE materials used in implantable orthopedic devices can induce a harmful biological response, so the manufacturer should determine the biocompatibility "of all patient-contacting materials" present in the device. If the device uses identical UHMWPE materials and manufacturing processes—with a similar location and duration of contact—as a legally marketed device with a history of safe use, manufacturers may reference previous testing or literature. If the manufacturer can't identify such a device, they will need to conduct a biocompatibility risk assessment.

The FDA recommends shelf-life testing to support the device's proposed expiration date. Shelf-life testing should evaluate the packaging integrity for maintaining device sterility, as well as any changes to device performance or functionality. The guidance notes the shelf life of UHMWPE that has been irradiated and packaged in an inert environment can be "limited by the integrity of the packaging material."

Read the full guidance document here: www.fdanews.com/04-26-19-UHMWPE.pdf.
— Tiffany Winters

Abaxis Gets Warning Letter for Adulterated Potassium Diagnostic

Abaxis was hit with an FDA warning letter over changes it made to a potassium assay used with its chemistry analyzer device that caused the product to be adulterated and misbranded.

The agency said that the Union City, California devicemaker made modifications that altered the potassium diagnostic's calibration specifications and changed the performance of the device, for which the company received customer complaints.

The device requires a new 510(k) clearance, the FDA said, because the altered calibration raises "new issues of safety and effectiveness since a falsely low potassium result could lead to serious adverse consequences such as delay in treatment or no treatment" for high potassium in the blood.

The agency also noted CGMP deficiencies in the firm's quality system. For example, the firm made a change to its potassium test's calibration in October 2013 but neglected to provide evidence that it performed risk evaluation or established pre-approved acceptance criteria.

The potassium assay, which is designed for use with the firm's Piccolo Xpress chemistry analyzer, was found to be adulterated, as the Class III device had no approved application for premarket approval.

Read the full Abaxis warning letter here: www.fdanews.com/04-25-19-Abaxis.pdf.
— James Miessler

CDRH Provides Guidance On Quantitative Imaging Devices

CDRH released guidance on what information should be included in regulatory submissions for devices that generate quantitative imaging values.

The guidance provides a general approach for developing and defining technical performance information to include in premarket submissions for devices with quantitative imaging functions.

Most images require a trained physician to identify a certain structure or feature. Quantitative imaging extracts additional information from images in the form of numerical values, such as standard uptake values in nuclear medicine and volumetric measurements in tomographic imaging in magnetic resonance imaging.

Because quantitative imaging functions have a broad range of intended uses, it is often difficult to define universal criteria for achieving a well characterized quantitative imaging function and sufficient user information, the agency says.

In general, devicemakers should provide performance specifications for the quantitative imaging functions, supportive performance data to show that the quantitative imaging functions meet those performance specifications, and sufficient information for the end user to understand the values provided, the draft guidance says.

The recommendations apply to premarket applications, humanitarian device exemption applications, 510(k) submissions and de novo requests. The guidance document is applicable to all devices that generate quantitative imaging values across a wide range of imaging modalities, intended uses, levels of automation, and complexity of algorithms.

The guidance proposes best practices for technical performance assessments, such as defining relationships between the quantitative imaging functions and the measure/use conditions and determining performance metrics such as bias, precision, limits of detection, linearity and sensitivity.

Read the guidance here: www.fdanews.com/04-26-19-QuantitativeImagingGuidance.pdf.

APPROVALS

FDA Allows Marketing of ADHD Device

The FDA has given a green light for NeuroSigma's Monarch external Trigeminal Nerve Stimulation (eTNS) system, a non-drug treatment for pediatric patients with ADHD.

The cell-phone sized device generates a low-level electrical pulse and is attached, by wire, to a

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

Approvals, *from Page 7*

small patch on the patient's forehead. It is designed for home use under caregiver supervision.

The system is indicated for patients ages 7 to12 years old who are not currently taking prescription ADHD medication.

It is the first non-drug treatment for ADHD granted marketing authorization by the FDA. The system gained the CE Mark in November 2015

Konica Minolta's X-Ray Technology Receives FDA Clearance

The FDA granted 510(k) clearance for Konica Minolta's Dynamic Digital Radiography (DDR) technology, used to produce medical images that show movement.

The DDR technology depicts movement in a single exam and the images can be annotated and can include diagrams.

The X-ray technology shows clinicians the interaction between anatomical structures like tissue and bone with physiological changes over time. It is particularly useful for musculoskeletal and thoracic imaging.

FDA Clears SurModics' Sublime Sheath

The FDA granted 510(k) clearance to SurModics' Sublime guide sheath, a radial artery access device for use in coronary procedures.

Designed for kink resistance and strength, the flexible braid-reinforced device has a working length covered in hydrophilic coating, creating a lubricious surface. It includes a dilator and hemostasis valve with a side arm for flushing.

The device will be available in two lengths (120 and 150 centimeters) and two diameters (five and six French gage).

New York Authorizes Veracyte's Genomic Test for Patients

Veracyte received regulatory authorization from the New York State Department of Health for its genomic test for idiopathic pulmonary fibrosis (IPF).

The Envisia Genomic Classifier is the first commercially available test that doesn't require surgery to distinguish IPF from other interstitial lung diseases.

The genomic test uses RNA sequencing and machine learning to recognize the pattern of usual interstitial pneumonia, an indicator of IPF.

FDA Clears AliveCor's Electrocardiogram Device

AliveCor received 510(k) clearances for two new indications for its KardiaMobile electrocardiogram device that now detects the three most common forms of heart arrythmia.

The newly cleared indications are for slow heartbeat (bradycardia) and fast heartbeat (tachycardia). The product was previously cleared for detecting atrial fibrillation (AFib).

The device, which works with most smartphones, can now inform physicians and patients about non-AFib arrhythmias that indicate bradycardia or tachycardia.

The ECG monitor can also share its rhythm results via the Apple Watch, allowing for the preemptive detection and treatment of AFib.

FDANEWS
wcg market intelligence & insights

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

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

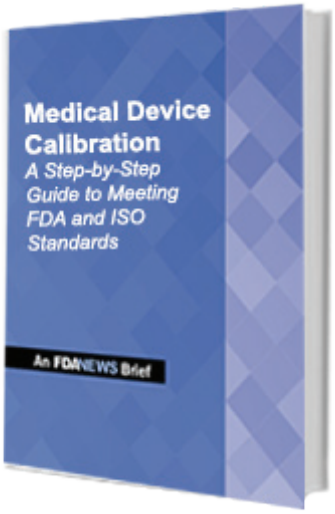
Ad Sales: Jim Desborough
+1 (703) 538-7647
jdesborough@fdanews.com

Multi-User Sales: Bailey Sterrett
+1 (703) 538-7637
bsterrett@fdanews.com

300 N. Washington St., Suite 200 • Falls Church, VA 22046-3431 • www.fdanews.com

Reporters: James Miessler, Bill Myers

President: Cynthia Carter



Medical Device Calibration: *A Step-by-Step Guide to Meeting FDA and ISO Standards*

Warning letter citing calibration failures are on the rise — indicating that the FDA is paying more attention to the issue.

Both the FDA and ISO have specific requirements for calibrating medical devices. And — they don't always line up. So devicemakers doing business in the US and abroad need a clear path to compliance if they want to avoid penalties.

Medical Device Calibration: *A Step-by-Step Guide to Meeting FDA and ISO Standards* provides a roadmap that walks devicemakers through each aspect of calibration requirements — showing where the FDA and ISO differ and where they match up — and explains how to combine them to endure full compliance.

You will learn:

- The role of monitoring and measuring in a medical device Quality Management System (QMS)
- Requirements for calibration in FDA's Quality System Regulation
- How to distinguish between accuracy and precision
- The role of traceability in a calibration program
- The audit requirements in both QSIT and MDSAP

The report defines key terms and concepts involved in calibration including proving that calibration practices can be traced back to recognized national and international standards.

FOUR EASY WAYS TO ORDER

1. **PHONE:** Toll free (888) 838-5578 or +1 (703) 538-7600
2. **WEB:** www.fdanews.com/55464
3. **FAX:** +1 (703) 538-7676
4. **MAIL:** FDAnews 300 N. Washington St., Suite 200 Falls Church, VA 22046-3431

☑**Yes!** Please send me ____ copy(ies) of ***Medical Device Calibration: A Step-by-Step Guide to Meeting FDA and ISO Standards*** at the price of $197 for each PDF.

Name _____

Title _____

Company _____

Address _____

City_____ State _____ Zip code _____

Country _____

Telephone _____

Fax _____

Email _____

METHOD OF PAYMENT

❑ Check enclosed (payable to FDAnews)

❑ Bill me/my company. Our P.O.# _____

❑ Charge my credit card:
❑ Visa ❑ MasterCard ❑ American Express

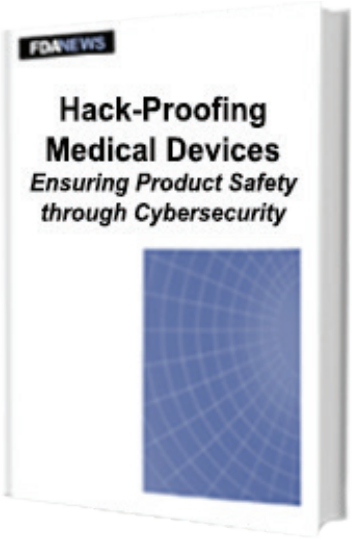
Credit card no. _____

Expiration date _____

Signature _____
(Signature required on credit card and bill-me orders)

Virginia customers add 6% sales tax.

19FLYR-N



Hack-Proofing Medical Devices: *Ensuring Product Safety through Cybersecurity*

How does the FDA expect you to fight cyber incursions?

With the recent release of the final guidance on postmarket management of cybersecurity, you now have advice from the agency.

The key is awareness — of product vulnerabilities, current threats, developments in cybersecurity protection, how to defend your company from disastrous liability litigation… and the list goes on.

Hack-Proofing Medical Devices will show you how to get — and keep — control of your devices' networked operations. The management report covers:

- Six environmental stressors that contribute to cybersecurity problems
- The overwhelming magnitude of the problem — 68,000 medical devices were found to be freely accessible through the Internet in 2015
- How the FDA and international regulators are handling issues involving software as a medical device (SaMD)
- Types of cybersecurity threats, including ransomware and device piggybacking
- And much more!

BONUS — the report also provides a variety of tools including:

- A checklist for verifying a device's cybersecurity controls status
- A sample medical device cybersecurity policy
- Spreadsheets that help assess level and severity of risk

Order your copy of **Hack-Proofing Medical Devices** and understand the nature of cybersecurity threats, how and where they occur and what you can do to prevent outside interference.

FOUR EASY WAYS TO ORDER

1. **PHONE:** Toll free (888) 838-5578
   or +1 (703) 538-7600
2. **WEB:** www.fdanews.com/54373
3. **FAX:** +1 (703) 538-7676
4. **MAIL:** FDAnews
   300 N. Washington St., Suite 200
   Falls Church, VA 22046-3431

☑**Yes!** Please send me ____ copy(ies) of ***Hack-Proofing Medical Devices*** at the price of $397 for each PDF.

Name _____

Title _____

Company _____

Address _____

City_____ State _____ Zip code _____

Country _____

Telephone _____

Fax _____

Email _____

METHOD OF PAYMENT

❑ Check enclosed (payable to FDAnews)

❑ Bill me/my company. Our P.O.# _____

❑ Charge my credit card:
❑ Visa ❑ MasterCard ❑ American Express

Credit card no. _____

Expiration date _____

Signature _____
(Signature required on credit card and bill-me orders)

Virginia customers add 6% sales tax.

19FLYR-N