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FDA Says All Off-Label Communications Can Fall Within Regulatory Purview

The First Amendment does not protect device makers from FDA oversight of off-label communication even if what they say is truthful, according to a Jan. 17 agency memo.

The FDA has the authority to regulate all off-label communication to ensure unapproved medical products do not reach the market, the memo said.

The agency cannot explicitly restrict communication on off-label uses, but it has the power to regulate the introduction of unapproved, uncleared, or misbranded products — including devices — into the market, as well as a company's promotions.

In the memo, the FDA dismissed arguments made in favor of loosening restrictions on off-label communications during a public meeting in November. The meeting was convened to involve stakeholders in the framing of guidance and regulations on the communication of unapproved uses.

The FDA clarified that its oversight applies to all off-label communication, even truthful or potentially misleading statements. Specifically,

(See **Off-Label***, Page 2)*

FDA Offers Examples of Communications Consistent with Approved Labeling

The FDA has released a list of examples of product communications consistent with agency-approved labeling for medical devices.

In draft guidance, the agency said sponsors may include information on safety and efficacy, including clinical trial data. The FDA said it considers labeling information on adverse reactions and a product's effect in a subpopulation to be appropriate.

The agency emphasized that sponsors may not include information about unapproved uses. For example, a device that is cleared to diagnose a specific gene mutation for individuals with cystic fibrosis should not include information about its use for individuals who do not have the disease.

(See **Labeling***, Page 4)*

Off-Label, *from Page 1*

the agency is allowed to regulate non-misleading communication when the enforcement substantially advances the government's public health interests.

The memo also pointed out limitations in 12 proposed approaches the FDA could take to make its oversight of off-label communication less restrictive, while still preserving the government's interests to promote public safety. The proposed approaches include:

- Prohibiting all unapproved uses;
- Creating ceilings or caps on the number of prescriptions for an unapproved use;
- Limiting Medicare and Medicaid reimbursement to approved uses;
- Prohibiting specific unapproved uses that pose safety concerns or developing tiers based on level of safety risk, with greater regulatory controls on riskier devices;
- Requiring firms to list all potential indications for a device in the initial premarket application;
- Allowing firms to actively promote an unapproved use as long as they disclose that the use is unapproved and include other appropriate warnings;
- Taxing firms more heavily for sales of devices for unapproved uses than for approved uses; and
- Permitting the promotion of unapproved uses listed in medical compendia.

The approaches do not strike a balance between the government and industry's interest, the agency said, and it invited stakeholders to offer alternatives.

In addition, the FDA issued draft guidance on communications by firms to payors regarding investigational devices. The agency does not intend to object to the following types of information about such devices:

- Product information such as device design;
- Information about the indication sought, such as information from the clinical study protocols about endpoints being studied and the patient population under investigation;
- Factual presentations of results from clinical or preclinical studies;
- The anticipated timeline for possible FDA approval/clearance;
- Product pricing information;
- Targeting/marketing strategies; and
- Product-related programs or services.

The guidance says firms should inform payors that the product is under investigation and that its safety and effectiveness have not been established, as well as the stage of product development or review status.

Payors should not be told that an investigational product is FDA-approved/cleared or otherwise safe or effective for the purposes for which it is under investigation.

The FDA also released draft guidance that listed examples of communications — including promotional materials — consistent with the agency-approved label. In that guidance, the agency cautioned device makers not to promote devices for unapproved uses.

Read the memo here: www.fdanews.com/01-18-17-FDAMemo.pdf.

Read the draft guidance here: www.fdanews.com/01-18-17-DraftGuidance.pdf.

Malaysian MDA Issues Guidance On Device Product Changes

Malaysia's Medical Device Authority has issued new guidance to manufacturers on regulatory requirements for making changes to registered medical devices.

Evidence of safety and effectiveness must be adequately documented before the authority will allow the device to stay on the market and the documentation required depends on the type of change. Changes that affect safety and performance require manufacturers to apply for a new device registration.

The guidance includes tables with examples of device changes and the documents that must be submitted to support them.

Read the guidance here: www.fdanews.com/01-13-17-MDAchangeguidance.pdf.

FDA Cites 22 Failed Trials, Makes the Case for Phase III

The FDA has compiled 22 case studies — including for two medical devices — that showed promise in Phase II clinical trials but later failed in larger Phase III trials.

The agency restated the importance of maintaining large, randomized, controlled trials, although the industry is increasingly interested in using alternatives to expensive Phase III trials and in using surrogate endpoints for accelerated results.

Despite good results at the Phase II stage for one device, Broncus Technologies's Exhale drug-eluting stent, used to improve airflow in patients with emphysema, in Phase III the stent failed to improve lung function or symptoms, the FDA said.

The report also cited the Co-Star drug-eluting coronary stent. A small clinical study conducted outside the U.S. suggested that it performed as well as other marketed stents. However, a clinical trial of 1,700 patients in the U.S. to support an application for FDA approval showed a significantly higher rate of cardiac problems at eight months compared with other stents.

Fourteen of the 22 studies were unable to confirm effectiveness, one was unable to confirm safety, and seven were unable to confirm both safety and effectiveness, the agency found. Two Phase III studies found an increased frequency of the problem the product intended to prevent.

"Phase III trials help care providers understand when a medical product provides clinical benefit to patients that outweigh the risks," the FDA said. "They also help researchers understand when a purported mechanism of action is credible and merits further development."

The full report is available here: www.fdanews.com/01-19-17-FDAPhase2_3TrialDivergence.pdf. — Conor Hale

Pemco Lands Form 483 For Correction and Removal Actions

Pemco Inc. received a Form 483 when inspectors found it had not submitted timely correction and removal and MDR reports, and had committed other violations.

FDA inspectors visited Pemco's Independence, Ohio, facility in October 2016 and discovered that a report of the required information regarding device correction and removal actions was not sent to the FDA within 10 days of initiating the correction or removal. Specifically, when a retractor device was returned for service on May 14, 2013, Pemco found the cover plates were improperly heat-treated and contaminated with carbon. It concluded that a removal would be performed but did not submit this correction/removal to the FDA until June 27, 2013.

In addition, an MDR report was not submitted within 30 days of learning that the ratchet assembly of a retractor had malfunctioned on two occasions and would be likely to cause or contribute to a death or serious injury if the malfunction were to recur.

Inspectors also found that non-conforming products were not adequately controlled. Pemco initiated Nonconforming Product Report due to undersized and oversized extender bar adapters. Based on the report, it was unclear how many products were actually non-conforming, which products were approved for rework, and if all non-conforming products were accounted for. Additionally, the company did not formally identify an area for non-conforming products in accordance with its procedures.

Finally, the company failed to document which testing equipment was used when measuring dimensional specifications and had not validated its cleaning processes for finished devices.

Read the Form 483 here: www.fdanews.com/01-12-17-Pemco.pdf.

Treasury Department Eases Sanctions On Medical Device Exports to Iran

The U.S. Treasury Department has recently expanded the range of medical devices that may be exported or reexported from the United States to Iran without the need for specific authorization from the department's Office of Foreign Assets Control (OFAC).

OFAC has established a new list of medical devices requiring specific authorization which includes a range of products from biocontainment chambers to HEPA filters. Other than the listed products, medical devices classified as EAR99 under the U.S. Export Administration Regulations are now generally authorized for sale and export to Iran.

"This new list represents a significant change in OFAC's approach for Iran with respect to the licensing of medical devices classified as EAR99," says Margaret Gatti, a partner in the International Trade and Sanctions Practice at Morgan Lewis.

The final rule also expanded general authorizations to include training, replacement parts, software, and services for medical devices.

Read the final rule here: www.fdanews.com/01-17-17-IranianFinalRule.pdf.

Read the full list of devices requiring specific authorization here: www.fdanews.com/01-17-17-IRANglmedsupplies.pdf.

FDA Reclassifies Influenza Test Systems as Class II

The FDA has reclassified antigen-based rapid influenza virus antigen detection test systems (RIDTs) from Class I to Class II devices and has introduced special controls aimed at improving the quality of testing.

There is evidence that the currently available antigen-based RIDTs, which are widely used in non-clinical laboratory settings, are performing poorly, resulting in many misdiagnosed cases, the agency said.

In addition to requiring premarket notification, the final order requires special controls that:

- Identify the minimum acceptable performance criteria;
- Require use of an FDA-accepted comparator method for establishing the performance of new antigen based RIDTs;
- Require annual analytical reactivity testing of contemporary influenza strains; and
- Require analytical reactivity testing of newly emerging strains under certain situations involving an emergency or potential for an emergency.

Manufacturers whose currently legally marketed devices do not meet the minimum performance criteria have one year to submit a 510(k) for a new or significantly changed or modified device.

Read the Federal Register notice here: www.fdanews.com/01-13-17-Influenza.pdf.

Labeling, *from Page 1*

Device firms also should consider whether a modification to the indications for use would trigger the need for a new premarket submission. If the information a firm wants to communicate represents such a modification, it would not be consistent with the agency's labeling policy.

In the draft guidance, the FDA explains the criteria it uses to determine whether a company's communication is consistent with an agency-approved label. First it looks at whether the indication, patient population, and directions for use are inconsistent with the device label. Next it evaluates whether the communication increases the potential for health risks. In particular, it looks at whether the communication modifies the benefit-risk profile. Lastly, the agency assesses whether the indications represented in the communication allow for safe and effective use based on the label's directions.

Read the draft guidance here: www.fdanews.com/01-17-17-CommunicationGuidance.pdf.

Industry Groups Question the FDA Approach to Software as a Medical Device

Draft guidance circulated by the FDA on software as a medical device (SaMD) might not fit well into the agency's regulatory regime, according to written comments submitted by two industry groups.

The FDA released the draft guidance on SaMD — which was prepared by the International Medical Device Regulators Forum (IMDRF) — for public comment Oct. 14, 2016. The document outlines steps required to generate clinical evidence of effectiveness and safety of SaMD products. As of last week, the agency had logged 58 comments on the draft.

AdvaMed said the draft guidance uses some terms that have particular meanings in the EU or that are specific to FDA regulations, and which do not necessarily translate across jurisdictions. For example, the term "clinical evaluation" is usually associated in the EU with a clinical evaluation report prepared to support marketing of a product — but not in the U.S. Use of the term would cause confusion and could lead other regulatory authorities to implement documentation requirements that are not intended, the group said.

Because there is no mechanism for independent review of SaMD in most jurisdictions, references in the document to independent review should be removed, AdvaMed said. Whether or not an independent review is needed should be based on local regulatory requirements, it added.

The association also criticized the draft guidance because it:

- Is based on risk categories that do not align with FDA's regulatory framework, requires data that is inconsistent with 510(k) requirements, and does not explain how the data will be incorporated into FDA regulations;
- Uses terms that are defined in prior IMDRF documents but have not been adopted through good guidance practices;
- Incorporates a number of IMDRF and Global Harmonization Task Force documents that have not gone through FDA notice and comment; and
- Uses definitions for clinical validity, scientific validity, and other terms that are similar to those used for in vitro diagnostics but are not consistent with either FDA or EU definitions.

In a separate comment, the 510(k) Coalition noted that because the draft guidance was prepared through the IMDRF, many U.S. stakeholders might not previously have had a chance to comment on it. IMDRF deliberations are not open or transparent, the group said. Before an IMDRF document can be turned into an FDA guidance document, it should be reviewed in public meetings and should be converted to U.S. format and wording, it said.

The coalition also questioned the connection between the draft guidance and U.S. regulatory requirements, noting the guidance does not include specific references to U.S. statutes or regulations. — Jeff Kinney

Upcoming Medical Device Meetings in 2017

Feb. 7-9, 2017
MD&M West 2017
Anaheim, CA
mdmwest.mddionline.com/

March 8-9, 2017
MDMA FDA Forum: PMA/510(k) Workshop
Palo Alto, CA
www.medicaldevices.org/events/EventDetails.aspx?id=886687&group=

March 9-10, 2017
Conducting Advanced Root Cause Analysis and CAPA Investigations
Raleigh., N.C.
www.fdanews.com/capapc

March 28-30, 2017
Medical Device Quality Congress
Bethesda, MD
www.fdanews.com/mdqc

(See **Meetings**, *Page 6)*

Zimmer Biomet Hit With 58-Page Form 483 Citing 14 Observations

Zimmer Biomet's Warsaw, Ind., medical device facility was hit with a massive, 58-page Form 483 arising from an inspection carried out from September to November of 2016.

In 14 observations — including 2 repeat observations first found in a 2014 inspection — the 483 listed numerous problems with validation of processes, inadequate environmental monitoring, water quality, product design, and other issues. The repeat observations were for inadequate validations and cleaning process monitoring.

The company's standard operating procedures failed to ensure that nonconforming products were consistently documented and evaluated, the inspectors found.

In addition, Zimmer did not have adequate procedures for corrective and preventive actions. For example, one of its procedures did not establish requirements for analyzing data sources. The corrective actions did not prevent quality issues from recurring, and there were no established procedures for investigating the cause of nonconformities.

The inspectors also reported inadequate process control procedures. For example, packaging operations were not adequately controlled

Read the Form 483 here: www.fdanews.com/01-19-17-ZimmerBiomet483.pdf.

Meetings, *from Page 5*

April 10, 11-13, 2017
2017 Design of Medical Devices Conference
Minneapolis, MN
www.dmd.umn.edu/

April 25-27, 2017
The Medtech Strategist Innovation Summit
Dublin, Ireland
www.medicaldevices.org/events/EventDetails.aspx?id=808698&group=

May 23-24, 2017
Digital Health World Congress
London, England
digitalhealthcareworldcongress.com/agenda/

BRIEFS

EU Grants CE Mark for Intact Vascular's Tack Endovascular System

Wayne, Pennsylvania–based Vascular Tack has attained the CE Mark for its Tack endovascular system for repairing arterial dissections following percutaneous transluminal angioplasty (PTA) below the knee.

The design of the device implant allows it to be used in arteries ranging from 1.5 mm to 4.5 mm in diameter. Unlike stents, which have to be precisely sized to the artery where they will be placed, the device adapts to the diameter of the artery.

FDA Clears SpineGuard's DSG Integration Module to Market

SpineGuard has received FDA marketing clearance for its DSG (Dynamic Surgical Guidance) integration module for use in combination with Zavation's spinal fusion system.

A DSG-enabled screw is a combination of a bipolar sensor and a pedicle screw in one device. The technology offers surgeons real-time guidance and the ability to insert the screw directly into a vertebra without drilling a pilot hole.

The DSG sensor differentiates various tissue types based on the analysis of the local electrical conductivity. Real-time feedback informs the surgeon of changes in tissue type by an audio signal varying in pitch and cadence. This alerts surgeons to potential breaches during screw placement.

Medasense Biometrics Nabs CE Mark for Pain Monitoring System

The European Commission has awarded a CE Mark for Medasense Biometrics' pain monitoring device, PMD200.

This device allows post-operative care units to adjust the treatment of pain by avoiding the use of excess or deficiency of analgesics that may cause major complication. The system consists of a finger probe that receives and measures physiological signals from four different sensors. This data is then analyzed by algorithms and converted to reflect a pain index score.

MindChild Acquires FDA Marketing Clearance for Fetal Monitoring System

MindChild Medical has received marketing clearance for its Meridian M110 non-invasive fetal heart monitor.

The device measures and displays fetal heart rate, maternal heart rate, and uterine contractions, using abdominal surface electrodes to detect the fetal ECG, maternal ECG and uterine contractions.

FDA Grants Marketing Clearance To CyMedica Muscle Stimulation Device

Scottsdale, Arizona–based, CyMedica Orthopedics has received FDA marketing clearance for e-vive, a wireless muscle stimulation device that rehabilitates muscle strengthening for ACL and total knee replacement patients.

The device system is app-controlled and allows patients to be engaged with their rehab by tracking their progress and allowing data-sharing to clinicians.

Medtronic Wins CE Mark For 34mm Heart Valve

Medtronic has won a CE Mark for its CoreValveEvolut R 34 mm valve.

The Evolut R 34 mm valve is approved for severe aortic stenosis patients who are at intermediate, high or extreme risk for surgery with a diameter size ranging from 26-30 mm.

The valve is designed to fit in the native aortic valve and is delivered through the EnVeo R delivery catheter system.

Ventripoint Applies to Health Canada For Heart Analysis System

Toronto, Ontario–based, Ventripoint is seeking Health Canada's approval for the expansion of its VMS heart analysis product to include the right atrium, left atrium and left ventricle chambers of the heart.

The expanded approval would allow the product to be used to determine the volume and function for all four chambers of the heart.

Cybersecurity Evaluations Will Focus on Patient Harm

In a move that could simplify compliance for devices at risk from cyber threats, the FDA said it will evaluate risk based on the potential for patient harm rather than on clinical performance.

In its final guidance on post-market cybersecurity management in medical devices, the agency said the change from the draft guidance — which focused more on essential clinical performance — could make life easier for manufacturers.

The patient harm focus "appears to be more straightforward and in line with standards that the device industry is already used to," said attorney Allyson Mullen of Hyman, Phelps & McNamara.

Despite the agency's emphasis on patient harm, manufacturers will still need to account for clinical performance, said Joseph Ouellette, an independent consultant with EAS Consulting Group. "You really have to consider both," he said. Companies spend a lot of time designing products, but "now that devices can be hacked and can potentially hurt somebody," they have to take the possibility of patient harm seriously.

The Dec. 28 final guidance offers four examples in which a device manufacturer learns of a cybersecurity vulnerability after a device has been commercialized. In all the examples, the risk of patient harm is controlled — meaning acceptably low — and the resulting software patch to address the cybersecurity vulnerability does not need to be reported to the FDA. The agency does not offer examples of when the risk is uncontrolled and reporting would be required.

Based on the four examples, it appears that manufacturers will need to consider cybersecurity vulnerabilities in their legacy products, Mullen said. However, the final guidance is not specific about whether or how the FDA will enforce cybersecurity in medical devices in the post-market setting.

The overall effect is to put manufacturers on notice that the FDA is taking cybersecurity very seriously, Ouellette said. "Unfortunately, products that sustain life are probably most susceptible," he said.

Read the final guidance here: www.fdanews.com/12-28-16-CybersecurityGuidance.pdf.
— Jeff Kinney

Nuvasive Gets Form 483 For CAPA Procedures

Nuvasive received a Form 483 for failing to establish adequate corrective and preventive action (CAPA) procedures and failing to document process validation activities and results.

After an October 2016 inspection of Nuvasive's Fairborn, Ohio, facility, inspectors reported problems with the company's CAPA procedures. In particular, one out of 11 CAPAs reviewed did not include an effectiveness check.

In addition, a preventive action report was opened to correct an internal audit observation that retrospective validations did not have required information. The preventive action report was closed with no documented efficacy testing. The PAR also did not meet the definition of a preventive action because it was opened to correct a deficiency found during the internal audit.

Read the Form 483 here: www.fdanews.com/01-12-17-Nuvasive.pdf.

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GCP Questions, FDA Answers

What subject information are you allowed to collect under HIPAAA? Which members of the study's staff are allowed to dispense the investigational product to subjects? What do you do if your principal investigator resigns? What constitutes a "certified copy" of an electronic record?

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