INTERNATIONAL DEVICES & DIAGNOSTICS MONITOR

Vol. 4, No. 28
July 16, 2018

IN THIS ISSUE

Trump Tariffs Hurt Medical Device Manufacturers

The Trump Administration followed through on its threat to impose tariffs on Chinese made-products including medical devices on July 6, announcing a 25 percent tax on $34 billion worth of imported Chinese products.

Medical device manufacturers voiced their concerns saying the tax will increase consumer prices and limit research and development, especially among medical imaging manufacturers.

According to the Office of the United States Trade Representative (USTR), the decision to impose tariffs was made after a Section 301 investigation found that "China's acts, policies and practices related to technology transfer, intellectual property and innovation are unreasonable and discriminatory, and burden U.S. commerce."

On July 10, after China responded with its own tariffs on U.S. imports, the administration doubled down, proposing additional tariffs on another 6,000 Chinese products worth $200 billion.

(See **Tariffs**, *Page 2)*

FDA Releases Draft Guidances On Gene Therapies

The FDA unveiled six new draft guidances outlining its latest thinking on the rapidly evolving field of gene therapy including two that address the development of combination products and retinal disorder devices.

The draft guidances deal with chemistry, manufacturing and control information for investigational new drugs including combination products, as well as retinal disorders, hemophilia, rare diseases, long-term follow-up, and testing of retroviral vector-based therapies.

The CMC guidance outlines the necessary components of a gene therapy IND, including labeling and environmental analysis, noting that sponsors must provide a list of all materials used in

(See **Guidances**, *Page 4)*

Tariffs, *from Page 1*

A spokesperson for AdvaMed told FDAnews that the group is 2"continuing to review the list of products affected" by the July 10 announcement, but unlike the July 6 list, the new list appears to have "minimal impact" on medtech.

Patrick Hope, executive director of the Medical Imaging and Technology Alliance (MITA), told FDAnews that "we are advising imaging stakeholders to help us stress with the administration that any trade imbalances and inequities between the U.S. and China have nothing to do with medical imaging devices. Medical imaging devices as a whole should be exempted so research and development can be encouraged. These tariffs should be halted immediately by a needed exemption to avert long-term damage to American innovation."

In a May 10 letter to United States Trade Representative Robert Lighthizer, Hope called the tariffs a "double-tax on manufacturers" and called on policymakers to "act quickly to ensure that patient access to innovative life-saving technology is not compromised."

The U.S. imports around $6 billion in medical technology from China, while China imports about $4 billion in U.S. medical technology, according to Brandon Henry, an analyst with RBC Capital Markets.

Industry insiders including AdvaMed have been pushing since the spring, when the idea of imposing a tariff on Chinese imports was first floated, to exclude medical devices from the list of products to be affected by the tariff. They had some success, reducing the amount of medical technology affected by the first tranche of tariffs from $2.8 billion to $836 million, according to Ralph Ives, AdvaMed's executive vice president of global strategy and analysis. Artificial joints and teeth were excluded from the first round of tariffs, as were defibrillators and hearing aids.

Still, many common devices were affected, including magnetic resonance imaging (MRI) and computed tomography (CT) equipment, x-ray equipment and ultrasound devices. MITA asked that medical imaging devices be excluded from the sanctions "as a humanitarian good."

Hope noted that the sanctions amount to a double tax on U.S.-based manufacturers, serving as a disincentive to manufacture medical devices in the United States. "A substantial proportion of the trade impacted by the proposed tariffs would simply be inter-company trade," explained Hope. "That is—the shipment of components between two manufacturing facilities owned by the same exact company." Under the current system, many products are imported from a manufacturer in China to their manufacturing facility in the United States, where they are transformed and re-exported—often to China—resulting in a tax to products on both ends of the supply chain.

Following a survey of medical imaging device manufacturers, MITA concluded that the cost of the Section 301 tariffs to U.S. devicemakers will be more than $138 million this year. Of those that responded to the survey, 100 percent said they would need to reduce their workforce as a result of the tariffs. Respondents also said they would either cut funding for research and development or pass on the 25 percent price increase to their customers.
— Donna Scaramastra Gorman

BRIEFS

Shanghai FDA Expands Medical Device Pilot Program

Shanghai FDA is expanding a pilot program for accelerating medical device registrations.

The pilot program was previously available to the Free Trade Zone in Shanghai's Pudong district. Medtronic participated in the pilot program along with four other companies that saw their devices enter the priority registration channel.

More than 20 companies are actively participating in the pilot that is being extended to all of Shanghai.

Japan Highlights Regulatory Risks Of Medical Applications for AI

An expert group created by Japan's Pharmaceuticals and Medical Devices Agency highlighted some concerns about the use of artificial intelligence in medical applications in a new paper published in the journal Advanced Biomedical Engineering.

AI-based systems using diagnostic images have "already surpassed the performance of human radiologists," and machine learning has "enormous potential" in many applications, the PMDA Science Board's AI subcommittee reported. But the subcommittee also cited concerns about the human-computer relationship and how this might impact medical care applications.

A core concern is that AI systems are capable of changing their performance through learning and this raises regulatory issues for the performance criteria.

The authors asked whether new registrations would be required if an AI system advanced itself and the challenges this would pose for manufacturers. A performance change may not always be positive, as it "may be worsened by improper learning," they said.

Another major risk for devicemakers is the unpredictability of the AI output "due to the black box nature of the machine learning algorithms."

The quality, efficacy and safety considerations for AI medical systems for their intended uses are just as important as for conventional medical devices, but "introducing AI-based technology may pose additional hazards not seen in the conventional medical devices and systems," they said.

South Korea Releases Device Cybersecurity Risk Management Guidelines

South Korea published new guidelines on cybersecurity risk management for medical devices.

The Medical Security Guide mirrors the approach taken by the FDA and references the UL 2900 medical device cyber security standard along with other standards such as ISO/IEC 27002 and NIST 800-53.

It aims to establish a safe, smart medical service environment for medical information security officers and medical device manufacturers.

The guide covers medical devices, gateways, networks and medical information systems and proposes classification and component-specific requirements to address security threats.

Medtech Europe Cites REFIT Program as EU Governance Model

The Industry4Europe coalition, which represents 122 industry groups including Medtech Europe, released a joint policy paper calling for "informed dialogue" between the industry, decision-makers at EU, national, regional and local levels, as well as the civil society. The coalition cited the European Commission's Regulatory Fitness and Performance (REFIT) program aimed at keeping EU law simple and removing unnecessary burdens as a particularly effective model.

The coalition proposes to adapt the REFIT program for industry to ensure that the competitiveness of the European industry is taken into account in all EU proposals to develop "an innovative and smart regulative framework with a long-term perspective."

The REFIT program includes a government group, with one seat per EU member state, and a stakeholder group made up of representatives of business, social partners and civil groups.

FDA Shoots Down Petition on Tyvaso Referencing Combination Products

The FDA denied a United Therapeutics petition urging the agency to reject ANDAs for combination products referencing the company's hypertension drug Tyvaso (treprostinil).

In its February petition, United Therapeutics asked the FDA not to approve an ANDA for products referencing Tyvaso unless the application specifically requests approval for a delivery device to be used with and approved as part of the proposed generic, unless it demonstrates that the proposed device component has the same critical design attributes and quality standards as the innovator device, and unless it demonstrates bioequivalence to Tyvaso.

The company submitted four similar petitions since 2016 regarding ANDAs that reference Tyvaso, but the agency denied all four on the grounds that it had not made a final decision on any applications that would be affected.

The FDA does not interpret the Food, Drug and Cosmetic Act as "requiring it to render a final decision within the statutory deadline on the approvability of specific aspects of ANDAs before a final decision on the approvability of any such ANDAs," the agency said.

Read the FDA's response to the petition here: www.fdanews.com/07-09-18-United.pdf. — Zack Budryk

---

Guidances, *from Page 1*

manufacturing and a description of the quality and control of the materials.

For submissions where the gene therapy is part of a combination product along with a device, sponsors should briefly describe that product in the summary and include the regulatory status of each component. To clearly distinguish the components, sponsors should include engineering and manufacturer information for the gene therapy and the drug/device in separate CTD submission entries.

In a second draft guidance, the agency addresses development gene therapies for retinal disorders, which in some cases consist of an implanted device. The draft offers several established efficacy endpoints, including best corrected distance visual acuity and rate of photoreceptor loss. For testing of retroviral vector-based human gene therapies, the FDA recommended testing material from multiple stages of product manufacture.

In a statement marking the release of the drafts, FDA Commissioner Scott Gottlieb said the agency plans to make full use of its expedited programs when reviewing gene therapy products.

Read the CMC and retinal disorder draft guidances here: www.fdanews.com/07-12-18-GeneTherapies.pdf. — Zack Budryk

Minnesota Devicemaker Hit For Procedural Issues

The FDA issued Summit Medical a Form 483, citing issues with CAPA and incoming product acceptance procedures as well as process validation shortcomings.

The Eagan, Minnesota-based device manufacturer's facility was inspected in late February. The agency found that the molding process used for numerous ventilation tube models was not adequately validated. The process was inadequate because no there was no product that met the requirements under the firm's parameters. In addition, there was no mold qualification for a particular tube component.

The firm also failed to adequately establish CAPA procedures. The firm initiated corrective actions after receiving a previous Form 483, completing mold qualifications for ventilation tubes, and subsequently closed the CAPA after verifying effectiveness. However, the mold qualifications for certain part numbers contained results that failed to meet the requirements set forth by their engineering drawings, yet were deemed acceptable. The FDA ruled the CAPA to be ineffective.

In addition, the firm did not establish procedures for accepting incoming products. Certain inspection activities required to be performed for silicone tray inserts and mats were not documented.

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

Tips for Failure Investigations

Once companies have their CAPA teams in place and they have gathered, reviewed and analyzed company quality data and documentation and established CAPA policies and procedures, they are ready to begin failure investigations. A CAPA investigation is triggered when one of the quality metrics being monitored reveals a problem or a potential problem. The key objectives of investigations are:

- To determine if the observed result is valid. The beginning of most investigations, whether into complaints or out-of-specification test results, is to determine if there really is, or could be, an observed or reported nonconformity.
- To determine the probable causes of the problem and potential effects on tested products, other batches of that product and processes.

Each investigation should start with a strategy meeting. The lead investigator, who is typically the head of quality assurance, must determine whether the meeting should be formal or informal and what it should accomplish. The lead investigator also must decide who should participate. To maximize an investigation's effectiveness, the company should gather everyone who understands the situation, including both high-level experts and frontline staff. Participants might include individuals from engineering, R&D, laboratory, production or QA. Certainly, the type of incident or deviation will help dictate attendance. As always, facilitation and focus both remain key to an effective meeting.

The meeting should serve as a way to gather information and should address both issues of fact (what is known) and suspicion (potential root causes), yet take care to separate fact from opinion. During the meeting, team members must determine what additional information they require and from whom to get it; prepare to communicate with the appropriate stakeholders; and clearly define the next steps of the investigation. The company should fully analyze the situation before moving on and examining what factors contributed to the problem.

The individual team members should resist the tendency to work on their own, in a "silo." Unfortunately, such a tendency arises when people grow defensive about their functional areas. An adequate investigation calls for teamwork, with input and information from all affected areas.

The primary method for conducting investigations is called root cause analysis. Root cause analysis is a step-by-step method of investigation that should lead to the underlying cause of an incident or nonconformity that triggered a CAPA investigation. RCA provides feedback on a company's operational performance. Through its use, an organization can identify improvements that must be made to prevent and mitigate consequences to adequately control risk.

Excerpted from the *FDAnews* management report: *Creating QSR-Compliant CAPA Systems: A Practical Guide for Devicemakers*.

Devicemaker Sybaritic Flagged for Failing to Follow Consent Decree

The FDA cited device manufacturer Sybaritic of Bloomington, Minnesota following a Feb. 22 to March 7 inspection for failing to comply with the terms of a consent decree.

The firm had signed a consent decree of permanent injunction in January 2010 and the agency inspection found that it continued to market its products with unapproved health claims even though the decree specifically prohibited it from designing, manufacturing, processing, packing, repacking, holding, distributing, importing or exporting any device.

When an injunction is granted, the FDA has a continuing duty to monitor the injunction and to advise the court if the defendants fail to obey the terms of the decree. If a decree is violated, the agency must consider a civil or criminal contempt of court, or other regulatory action.

Sybaritic makes a number of products for which it makes health claims. For example, it markets medical spas such as its Cocoon Wellness Pro that the firm said increases circulation and metabolism, removes toxins and helps manage weight loss.

It also markets the SaunaLux 360 infrared sauna, which the firm claims has healing and energy benefits. On its website, Sybaritic said that the SaunaLux 360 "harnessed the power of red chromotherapy," and made a number of claims that the red chromotherapy lighting increases vitality, strength, alertness, circulation and the body's natural healing properties. It also claimed the lighting helps heal colds, arthritis, sluggish conditions and stimulates blood flow, as well as stimulating and producing red blood cells.

Additional claims included cosmetic healing, cardiovascular health, decreased heart rate and kidney filtration due to reduced loss of electrolytes.

The 483 said the firm failed to comply with the consent decree because it did not provide a copy of the consent decree to new associates, including suppliers.

The company also failed to comply with the consent decree because it failed to notify the agency "before any creation or dissolution of subsidiaries, franchises, affiliates, or 'doing business as' entities."

Read the Sybaritic Form 483 here: www.fdanews.com/07-11-18-sybariticinc483.pdf.

AdvaMed Says Abbreviated 510(k) Guidance Needs More on Device Types

The FDA should clarify which device types will be eligible for its abbreviated 510(k) pathways, AdvaMed said in a written comment on the agency's draft guidance.

AdvaMed said the pathway will depend on forthcoming FDA guidances specific to each device type and that the agency should provide more details about how it intends to prepare the guidances.

The draft guidance says source criteria will come from FDA staff, literature, and data from existing devices, but it makes no mention of input from healthcare professionals and other stakeholders.

"Consulting with healthcare professionals and other stakeholders offers perspectives and expertise different from sources that FDA proposes to reference," AdvaMed said. To gather all the relevant information, "these parties require an opportunity to review and comment on device type performance criteria."

Read the full comment here: www.fdanews.com/07-12-18-AdvaMed.pdf.

483, *from Page 5*

Some supplies received by the facility were found to be nonconforming, and some were returned to the vendor. But some were used in the production and assembly of a product, the agency said.

Read the Summit Medical Form 483 here: www.fdanews.com/07-12-18-summitmedicalllc483.pdf. — James Miessler

Feminina Group Flagged For Significant Violations

A Seattle, Washington devicemaker drew a Form 483 after a March inspection by the FDA revealed the facility lacked procedures for medical device reporting and had other significant nonconformances.

The agency noted that The Feminina Group had no procedure for medical device reporting and its complaint procedures did not include an evaluation for MDR.

The firm also lacked a procedure for performing quality audits and had no documentation showing that quality audits were being performed. The investigator observed that the company had no procedure for performing management reviews and there was no any evidence of any management reviews being performed.

In addition, the firm indicated that it had no procedure for design control or corrective and preventive actions.

The facility's device history records did not include the quantity manufactured, primary identification labels or labeling used for each production unit. Also, the company could not provide a device master record for a product it manufactured.

The firm also indicated that it had no procedure for supplier control or purchasing, and no documentation showing the firm evaluated and approved its current contract manufacturer.

Read the Form 483 here: www.fdanews.com/07-12-18-thefemininagroupinc-483.pdf.
— James Miessler

APPROVALS

Renovis Gains FDA Clearance For Interbody Spinal Fusion System

Renovis won 510(k) clearance for its Tesera SA hyperlordotic anterior lumbar interbody spinal fusion system.

The porous, titanium implants feature a four-screw design and a locking cover plate to prevent the screws from backing out.

The implants are made using 3D printing, with a porous surface structure that enables in-growth and bone attachment to the implant.

Medtronic's Automated Insulin System Receives CE Mark

Medtronic's hybrid closed loop automated insulin system, which combines an automated insulin pump with a continuous glucose monitor, gained CE Mark approval.

The device uses a new sensor to achieve a fully closed loop system and it has a built-in algorithm to prevent glucose spikes and allow for better diabetes management.

The new sensor, which is 80 percent smaller than its predecessor, uses a battery that has been improved to last seven days instead of six.

Hologic's MRSA Assay Receives CE Mark in Europe

Hologic's Panther Fusion MRSA assay received CE Mark approval in Europe.

The assay detects and differentiates between Staphylococcus aureus and methicillin-resistant Staphylococcus aureus DNA by analyzing nasal samples.

The assay is capable of identifying empty a broad range of strains.

Tenon Medical's Joint Fusion System Cleared by FDA

The FDA granted 510(k) clearance for Tenon Medical's Catamaran sacroiliac joint fixation system.

The system is indicated for conditions including sacroiliac joint disruptions and degenerative sacroiliitis, common causes of pain in the legs, lower back and the sacroiliac joint.

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

Approvals, *from Page 7*

The device allows surgeons to choose between using a navigated procedure or fluoroscopic imaging while the implant is designed to allow for bone graft materials to be loaded and delivered before and after placement.

Axonics' Implantable Neurostimulator Receives CE Mark

Axonics was granted a CE Mark for its sacral neuromodulation external trial system, used in treating patients with urinary and bowel dysfunction.

The external trial system consists of a temporary, single-use stimulator that is connected to either a tined lead or peripheral nerve stimulator lead, depending on the trial method.

The trial system is an extension of the Axionics sacral neuromodulation system and is used to help identify patients responsive to sacral neuromodulation therapy before a permanent implant is installed.

ThermoFisher's Allergy, AutoImmune Testing Platform Gets CE Mark

ThermoFisher's Phadia 200, a benchtop instrument used to test for allergy and autoimmunity conditions, has received CE Mark approval.

The instrument, which quantifies clinically relevant antibodies in blood, is capable of performing up to 700 different ImmunoCAP and EliA tests. It can process 42 samples and produce up to 200 test results daily.

The device is meant to be used in smaller diagnostic facilities for the purposes of improving output and efficiency, and reduces the frequency of sending samples offsite for testing.

Oculocare's Alleye App Cleared for Monitoring AMD

Oculocare's Alleye, a mobile application was granted 510(k) clearance by the FDA for monitoring eyesight in age-related macular degeneration (AMD).

The app gives patients the ability to regularly test their eyesight and assess the progression of disease without the supervision of a doctor.

It is designed to detect and characterize visual distortion in patients with macular conditions such as AMD and diabetic retinopathy.

RedDress Receives Clearance For Wound Care Device

RedDress received 510(k) clearance for its wound care device, which allows health care providers to produce whole blood clots.

The device is intended to be used at point-of-care, using the patient's own peripheral blood to clot wounds.

Under professional supervision, the blood clot produced by the system is topically applied to manage exuding cutaneous wound such as ulcers and mechanically or surgically-debrided wounds.

IsoRay's GammaTile Cleared For Treating Recurrent Brain Neoplasms

IsoRay it received 510(k) clearance for its GammaTile therapy, a device that treats recurrent brain tumors.

The device uses proprietary Cesium-131 seeds within customizable collagen-based carriers to treat the tumors, delivering a fast-acting therapeutic dose near the tumor bed.

FDANEWS

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

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

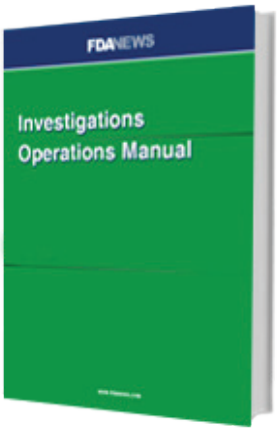
Ad Sales: Jim Desborough
+1 (703) 538-7647
jdesborough@fdanews.com

Multi-User Sales: 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: Zack Budryk, James Miessler, Bill Myers

President: Cynthia Carter



Investigations Operations Manual 2018

The **Investigations Operations Manual** is the primary policy guide for FDA investigations and directs the conduct of all fundamental field investigational activities. Adherence to the manual is required.

Now you can have the same investigation manual for 2018 that the FDA investigators use.

Know what the investigators look for — before they even get there. Know the investigators' expectations and rights. Find and fix problems *before* they end up on a Form 483 or warning letter.

There is no better way to prepare for an inspection than studying the actual procedures the FDA teaches its investigators.

Available directly from FDAnews, the newly updated edition of the **Investigations Operations Manual 2018** is the primary source FDA investigators use to conduct field inspections.

Order today.

Get insider information on:

- Sampling techniques
- Import hold procedures
- Recalls
- Types of investigations
- And more…

Make sure you've got the *latest* version before the FDA knocks on your door.

FOUR EASY WAYS TO ORDER

1. **PHONE:** Toll free (888) 838-5578
   or +1 (703) 538-7600
2. **WEB:** www.fdanews.com/55983
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 **Investigations Operations Manual 2018** at the price of $377 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.

18FLYR-N

FDANEWS

EU MDR Compliance: *A Checklist for Meeting Manufacturing, Safety and Performance Requirements*

The new EU Medical Device Regulation is massive… complex… and confusing… and you must be ready to comply by May 26, 2020.

When the European Union revised its system of rules for medical device manufacturers in 2017, it replaced a longstanding set of directives on specific topics with one large document that covers all aspects of making devices in EU countries.

Not only did they consolidate all the rules, they gave them greater weight. Previously, medical device directives provided guidance but did not have the force of law. The new MDR, however, contains mandates that are legally enforceable by EU member countries.

The FDAnews report **EU MDR Compliance** can help. Our editors have combed through the regulations, picking out the most minute compliance points and building them into a checklist of 200+ requirements you can use to confirm that you are satisfying all the EU mandates for device manufacturing. The report provides:

- Definitions of key terms in the EU MDR
- Knowing where to find specific requirements in the 150+ page regulation
- Checklists that walk you through every aspect of manufacturing, safety and performance requirements
- A training tool for employees new to the regulations

EU MDR Compliance: *A Checklist for Meeting Manufacturing, Safety and Performance Requirements* is the tool that collects all the requirements, explains them and itemized them in an easy-to-use form to ensure compliance.

FOUR EASY WAYS TO ORDER

1. **PHONE:** Toll free (888) 838-5578 or +1 (703) 538-7600
2. **WEB:** www.fdanews.com/55623
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 ***EU MDR Compliance: A Checklist for Meeting Manufacturing, Safety and Performance Requirements*** 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.

18FLYR-N