MedWatch ◆ Drug/ Biologic Safety ◆ VAERS ◆ MDR/Device Tracking ◆ Corrections & Removals ◆ Complaint-handling ◆ Dietary Supplements ◆ Vigilance

Adverse Event Reporting *News*

The Biweekly Guide to the Reporting of Adverse Events for Drugs, Devices, Biologics & Dietary Supplements

Vol. XIII, No. 19 *October 18, 2016*

Drug review

FDA withdraws generics for Concerta methylphenidate hydrochloride extended release tablets by Mallinckrodt, Kudco

FDA is proposing to withdraw approval of two generic versions of Concerta (methylphenidate hydrochloride) extended-release (ER) capsules, used to treat attention-deficit hyperactivity disorder.

Mallinckrodt Pharmaceuticals and **UCB/Kremers Urban** (formerly **Kudco**), the companies that make the generic products, "have failed to demonstrate that their products provide the same therapeutic effect as (are bioequivalent to) the brand-name drug they reference," FDA said in its Oct. 17 announcement.

This action is related to steps FDA took in November 2014. At that time, FDA announced that, based on an analysis of data, it had concerns that the Mallinckrodt and Kudco products may not produce the same therapeutic effects as Concerta. FDA requested that Mallinckrodt and Kudco either voluntarily withdraw their products from the market and request that FDA withdraw approval of their product's Abbreviated New Drug Applications (ANDAs) or, within six months, provide data to confirm that their products are bioequivalent to Concerta consistent with the revised draft guidance for industry for bioequivalence testing for these products.

At that time, FDA changed the Orange Book therapeutic equivalence code for these two products from AB (indicating therapeutic equivalence) to BX (data are insufficient to determine therapeutic equivalence).

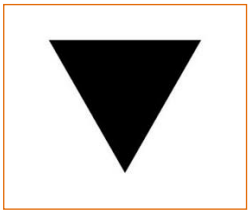
See Concerta, page 2

In This Issue

Vigilance

Royal Pharmaceutical Society releases new pharmacovigilance guidance using 'black triangle'

The **Royal Pharmaceutical Society** (RPS) has launched new guidance on the EU-wide scheme for the additional monitoring of medicines, commonly known in the UK as the "black triangle" scheme, Britain's "Pharmaceutical Journal" reported Oct. 6.



Pharmacists, other health care professionals and patients should report any suspected adverse reaction for medicines with a black triangle, the group announced.

See Triangle, page 2

Concerta, from Page 1

Neither Mallinckrodt nor UCB/Kremers Urban has voluntarily withdrawn its product from the market, and neither has provided data confirming its product's bioequivalence consistent with the revised recommendations.

Accordingly, FDA is proposing to withdraw approval of the products' ANDAs and is announcing an opportunity for the firms to request a hearing on the proposal. As part of this process, FDA is publishing Notices of Opportunity for Hearing (NOOHs) on its Proposals to Withdraw Marketing Approval in the Federal Register. If approval of these ANDAs is withdrawn by FDA, the products will no longer be able to be marketed in the U.S.

Each NOOH explains that the firm may request a hearing to show why approval of their ANDA should not be withdrawn and has the opportunity to raise, for administrative determination, all issues relating to the legal status of the drug products covered by these applications. Each firm must respond in writing, within 30 days, to request a hearing. If the firm fails to do so, the opportunity for a hearing will be waived.

During the course of this process, FDA will update the related Mallinckrodt and UCB/Kremers Urban dockets as new information becomes available.

The Mallinckrodt UCB/Kremers Urban products are still approved and can be prescribed, but they are not recommended as automatically substitutable for Concerta. **Janssen** manufactures an authorized generic of Concerta, which is marketed by **Actavis** under a licensing agreement. The Actavis product is not impacted by this announcement.

If you or your health care professional are concerned that a methylphenidate hydrochloride ER product you are taking is not providing the desired effect, and you do not know the manufacturer, contact the pharmacy where the prescription was filled to verify the product's manufacturer. If you, or those under your care, are taking the Mallinckrodt or Kudco products and have concerns about lack of desired effect during the dosing period, contact the prescribing health care provider to discuss whether a different drug product would be more appropriate.

FDA has not identified any serious safety concerns with these two generic products. Patients should not make changes to their treatment except in consultation with their health care professional.

Triangle, from Page 1

In collaboration with the **Assn. of the British Pharmaceutical Industry's** (ABPI) Pharmacovigilance Expert Network (PEN), the RPS has produced a quick reference guide and an "Advice for pharmacists" document highlighting the importance of the black triangle and explaining the ways in which health care professionals can contribute to medicines' safety by being vigilant and reporting any adverse reactions to black triangle medicines.

In the EU, a black triangle is usually assigned to a medicine for five years following initial authorization. It can then be reinstated at any later stage in a medicine's life cycle if there are safety concerns that require monitoring. The black triangle can be found next to the name of relevant medicines on the summary of product characteristics, patient information leaflet, in the British National Formulary or on advertising and educational materials for health care professionals and patients.

Pharmacists, other health care professionals and patients are encouraged to report any suspected adverse reaction for medicines with a black triangle. Reports can be submitted via the Yellow Card scheme and/or directly to the marketing authorization holder.

In a comment on the article online, it was noted "that there is also a Yellow card app available from the Apple app store or the Google Play store. This app can be used for reporting adverse events and it has other very useful features too." Below is a link to the Yellow card scheme page on the MHRA website where there is information on the app.
https://yellowcard.mhra.gov.uk/the-yellow-card-scheme/

ISCR hosts 3rd National Pharmacovigilance symposium in India

The **Indian Society for Clinical Research** (ISCR) recently held its 3rd National Pharmacovigilance (PV) Symposium on the theme "Evolving a Pharmacovigilant Environment in India - Collaborations, Opportunities & Challenges," **Pharmabiz.com** reported Oct. 4.

The symposium brought together pharmacovigilance stakeholders across biopharma industry, CROs, service providers, medical professionals, academia and regulators on a common platform to deliberate on the evolution of a pharmacovigilant environment in India by facilitating collaborative efforts to aid the emerging regulatory initiatives.

G.N. Singh, Drug Controller General of India, delivered the inaugural address during which he spoke about the government of India's initiatives to promote

pharmacovigilance through the **Pharmacovigilance Program of India** (PvPI) and invited stakeholders to share their knowledge with PvPI for furthering the cause of pharmacovigilance in India.

While delivering the guest of honor's address, N.K. Ganguly, Former Director General of India's Council of Medical Research, reiterated that more efforts have to go into building structured long-term collaborative ventures involving all stakeholders in order to benefit patients in India. Sessions covered during the symposium included the role of stakeholders in the evolving Indian pharmacovigilance environment, quality management in pharmacovigilance, pharmacovigilance in clinical trials and advances in pharmacovigilance.

ISCR is an association of clinical research professionals that aims to build awareness of clinical research as a specialty in India and to facilitate its growth in the country while helping to evolve the highest standards of quality and ethics.

Pharmacovigilance program of India asks research center to monitor adverse reactions

The **Pharmacovigilance Program of India** (PvPI), which has identified the **SDS TB Research Center, Rajiv Gandhi Institute of Chest Diseases** (RGICD) to monitor adverse drug reactions (ADRs), is now working to have a center for research and training, **Pharmabiz.com** reported Oct. 10.

The objective is to educate its nurses and doctors on early detection of ADR caused by TB and lung infection medications, according to the article.

The 470-bed teaching and government autonomous institute has two departments, Pulmonary Medicine and Thoracic Surgery, which treat infectious and contagious diseases besides related emergencies. Under PvPI, it also coordinates with other government hospitals and local DOTS (directly observed treatment, short-course) centers under the RNTCP (Revised National Tuberculosis Control Program) to source ADR information.

"We are an ADR monitoring center of PvPI since January 2013. Going by our efforts to report and record ADR besides transmit the data to PvPI via VigiFlow to the Uppsala Monitoring Center, Sweden, we are now looking at the next phase of growth in Pharmacovigilance," Shashidhar Buggi, M.D., director, SDS TB Research Center-RGIDC and coordinator, ADR Monitoring Committee, told Pharmabiz.

"Therefore we are planning to approach PvPI for an in-house research-training facility within the complex. Our intent is to moot an education drive to detect medication reaction early and its efficient management," he added.

ADR is a critical component in patient care, specifically for tuberculosis, where under DOTS drug regime medication reactions are common and widespread. Therefore, reporting it immediately and taking the right precautions saves the patient from unnecessary complications, said Buggi.

According to B. Dharini, M.D., pharmacovigilance associate, at SDS TB RC, the TB drug regime is vast. It includes first-line of oral drugs, injectables and fluoroquinolones, and oral bacteriostatics, which are second-line therapy. ADRs are obvious and could span from hearing loss to dizziness, rashes, anorexia, abdominal pain, nausea and vision loss among others. Immediate medical attention is required on a time-bound basis to stop the drug and control the reaction after which an alternate medication is prescribed.

"In order to further give a fillip to our current medication methods, we need to percolate this knowledge on ADR not just among physicians, but also among nurses and patients. We are keen to embark on pharmacovigilance research and training. There is also an increasing need to circulate banned drugs information across the hospital. We are looking to streamline the drug information access among physicians, nurses and patients. Therefore, we envisage the need for a dedicated center to encourage ADR reporting and evaluate casualties as faster pace," said Buggi.

International

EDQM enhances sharing of information with Japanese regulatory authorities, strengthens collaboration with Japanese Pharmacopoeia

The European Directorate for Quality of Medicines (EDQM) Oct. 3 said it has agreed with the

Japanese authorities to improve the sharing of information related to therapeutic products that are common to both Europe and Japan, and to strengthen collaboration between the European and Japanese Pharmacopoeias.

On Sept. 16, the Pharmaceutical Safety and Environmental Health Bureau of the Ministry of Health, Labor and Welfare (MHLW), the Pharmaceuticals and Medical Devices Agency (PMDA) of Japan and the EDQM exchanged letters that detail how communication between the parties will be enhanced, at the same time respecting the confidentiality of information that is not in the public domain. The sharing of information will concern mainly the outcome of GMP inspections of manufacturing sites of active pharmaceutical ingredients of interest to both Europe and Japan.

In addition, the EDQM and MHLW signed a five-year Memorandum of Cooperation that defines concrete measures for strengthening collaboration between the European and Japanese Pharmacopoeias (Ph. Eur. and JP, respectively). These include the option of organizing bilateral meetings, workshops and internships between the Ph. Eur., the JP and various Japanese regulatory bodies in either region/country, in order to share experiences and information on the development of monographs and methods of testing. To this end, the EDQM and MHLW also agreed to set up an ad hoc Technical Working Group involving staff members of the EDQM and Japanese regulatory bodies as well as relevant experts.

This strengthened relationship will enhance the ability of the MHLW, PMDA and EDQM to protect and promote the health and safety of the populations of their respective country/region. The constant aim of the partners will be to facilitate increased access to safe, effective and high quality products in Europe and Japan.

User fees

FDA to try to speed generic drug reviews and fees under GDUFA Reauthorization

FDA and representatives from the generic drug industry have reached an agreement in principle on proposed recommendations for the first reauthorization of the generic drug user fee program, FDA announced Oct. 17.

The agency published the draft agreement for public comment and will hold a public meeting on Oct. 21 to hear additional public comments. The final recommendations are scheduled to be delivered to Congress in January 2017.

As part of the second iteration of the Generic Drug User Fee Amendments (GDUFA), the draft commitment letter incorporates several lessons learned over the last five years. Industry stakeholders support the provisions in the draft commitment letter.

Major changes included in the draft commitment letter and user fee structure:

- Review of performance goals will be streamlined and consolidated;
    - All ANDAs and ANDA amendments would fall within a single, consolidated review goals scheme to simplify and streamline program administration, promote review efficiency, and ensure that "no submission is left behind"
    - GDUFA II would create faster review goals for priority submissions. For an ANDA, standard review would be 10 months from submission and priority review would be 8 months from submission.
- There will be a new pre-ANDA program, with product development, pre-submission and mid-review-cycle meetings;
- The user fee structure will be significantly restructured, helping to provide resources appropriate for our workload.
- The new user fee structure will address small businesses concerns;
    - A facility will not pay an annual facility fee unless it is identified in at least one approved generic drug submission
    - Contract Manufacturing Organizations, generally small businesses that are hired by ANDA sponsors to manufacture their generic drugs, would pay only one-third the annual fee paid by firms that manufacture under ANDAs which they or their affiliates own
    - A tiered generic drug applicant fee will feature a small tier (one to five approved ANDAs); the fee will be one-tenth of a full program fee.

This guidance also explains how GDUFA relates to Prior approval supplements (PAS) submissions. It also describes the performance metric goals outlined in the GDUFA Commitment Letter that FDA has agreed to meet, and clarifies how FDA will handle a PAS and amendments to a PAS for an ANDA subject to the GDUFA performance metric goals.

Click here to see the PAS guidance: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM404441.pdf

Drug safety

FDA places Regeneron and Teva's pain-drug study on hold

Regeneron Pharmaceuticals and partner **Teva Pharmaceutical** said FDA placed a clinical hold on a study testing their pain treatment, dealing another blow to companies looking to develop a safer alternative to opioid painkillers, **Reuters** reported Oct. 17.

FDA imposed the hold in the mid-stage trial in patients with chronic lower back pain, after a form of joint damage was observed in an advanced osteoarthritis patient who was given a high dose of the injectable drug, fasinumab.

The announcement suggests fasinumab will be plagued by the same limitations as other drugs in its class, including heightened scrutiny, repeated delays, and labeling restrictions, **Leerink Partners'** Geoffrey Porges said.

The treatment is designed to block nerve growth factor (NGF), a protein involved in transmission of pain signals.

Fasinumab has the potential to be an alternative to prescription opioids, that are effective for pain relief but are associated with high rates of addiction, overdose and death.

Following the FDA decision, Regeneron has completed an unplanned interim review of data and has stopped dosing patients, the companies said.

The analysis showed clear evidence of an improvement in pain scores in patients dosed with fasinumab, compared with placebo.

Regeneron was "lucky" to sell half the drug to Teva in a timely fashion," noted **Sanford C. Bernstein's** Ronny Gal.

The news of the hold comes less than a month after Regeneron announced the up to $1.3 billion deal with Teva to codevelop fasinumab.

The two drugmakers now plan to discuss with FDA a late-stage study for chronic lower back pain, excluding patients with advanced osteoarthritis.

Fasinumab is also being tested for use in osteoarthritis-related pain.

FDA staff flag concerns about Allergan's urinary drug

The proposed dosing for a drug being developed by **Allergan** to treat frequent urination at night has not been adequately studied in trials, a preliminary review by FDA staff concluded, **Reuters** reported Oct. 17.

The drug, SER120, is a low-dose nasal version of the commonly used treatment, desmopressin, and is designed to treat adults with nocturia, a disorder where a person wakes up to urinate twice or more at night.

Adverse Event Reporting *News*
Kenneth Reid, Editor & Publisher
Kathy Thorne, Subscriptions Dept.
Rebecca Mashaw, Associate Editor

Washington Information Source Co.
19B Wirt Street SW
Leesburg, VA 20175
(703) 779-8777 Fax: (703) 779-2508
Subscriptions: (301) 528-7777
Fax: (240) 599-7679
Internet: http://www.fdainfo.com
Email: service@fdainfo.com

There are no FDA-approved drugs to specifically treat nocturia.

Allergan has proposed starting patients with a 0.75 microgram (mcg) dose, and moving up to 1.5 mcg if necessary, but this dosing regimen was not studied in any clinical trials, staff reviewers said.

In addition, late-stage data showed that only the higher dose met the statistical criteria for efficacy. The "clinical meaningfulness" of the drug's benefit was also unclear when compared with a placebo, the reviewers said.

Desmopressin was first approved in the United States in 1978 to treat patients with diabetes insipidus, a rare disorder that causes an imbalance of water in the body.

Since then, FDA has sanctioned the drug's use in other conditions.

An oral desmopressin pill from privately held **Ferring Pharmaceuticals** has been rejected twice by FDA, which said the risk of hyponatremia, or abnormally low sodium levels in the blood, outweighed the drug's benefit.

FDA had asked Allergan to enroll patients aged at least 50 to better assess the risk of hyponatremia, which is greater in the elderly, in its late-stage trials for SER120. However, since the company is seeking approval for adults regardless of age, efficacy in patients younger than 50 has not been assessed, the staff said.

Of the five deaths among patients on SER120 during clinical trials, the role of the drug cannot be definitively ruled out in two, the reviewers said. Four of the five deaths were in patients older than 75.

Nocturia is a considered a symptom of one or more underlying conditions such as obstructive sleep apnea, diabetes mellitus and congestive heart failure.

FDA review confirms rivaroxaban's safety, efficacy in patients with atrial fibrillation

After a thorough review, FDA has concluded that Xarelto (rivaroxaban) is a safe and effective alternative to warfarin in patients with atrial fibrillation, according to the Oct. 12 **CardiovascularBusiness.com**.

FDA's Oct. 11 announcement came three months after **Alere** voluntarily recalled its INRatio and INRatio 2 devices, which were used to monitor warfarin in the ROCKET-AF trial. Results of that study, which compared warfarin and rivaroxaban, supported the FDA approval of rivaroxaban in 2011.

When Alere acknowledged that the INRatio devices could lead to inaccurate results, FDA performed several analyses to determine if the devices affected the findings of the ROCKET-AF study. FDA said in a news release that "effects on strokes or bleeding, including bleeding in the head, were minimal."

FDA has approved rivaroxaban to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation. The agency said no labeling changes would be needed due to issues with the INRatio devices.

EMA recommends measures to ensure safe use of Keppra oral solution; medicine should only be used with dosing syringe included in the package

Several measures have been put in place to ensure that the correct dosing syringe is used to measure Keppra oral solution, and thus avoid medication errors, the European Medicines Agency announced Oct. 14.

Keppra (levetiracetam) is a medicine for the treatment of epilepsy. It can be used on its own in patients from 16 years of age with newly diagnosed epilepsy, to treat partial-onset seizures with or without secondary generalization. It can also be used as an add-on to other antiepileptic medicines to treat partial-onset seizures with or without generalization in patients from one month of age; myoclonic seizures in patients from 12 years of age with juvenile myoclonic epilepsy; and primary generalized tonic-clonic seizures in patients from 12 years of age with idiopathic generalized epilepsy.

Keppra is available as an oral solution, as tablets and as a solution for infusion (drip) into a vein.

Several generics of Keppra are marketed in the European Union. Companies that market generic levetiracetam oral solutions are also expected to use

colors to differentiate one presentation from another, and to clearly indicate on the package and the label the age range of the child that the presentation should be used for, and which dosing device should be used.

In children, the dose of Keppra depends on the child's body weight and age, and the oral solution is the preferred formulation for use in children under six years of age. The medicine is available as a 100 mg/ml solution in either a 150 or 300 ml size bottle, and it comes with a 1-, 3- or 10-ml syringe.

Cases of accidental overdose have been reported with levetiracetam oral solution; the majority of cases occurred in children aged between 6 months and 11 years. Most of the cases occurred when the medicine was used with a wrong dosing syringe (e.g., a 10-ml syringe was used instead of a 1 ml one, leading to a 10-fold overdose), or because of a misunderstanding of the caregiver about how to properly measure the dose. Levetiracetam overdose often has no symptoms, but it may cause sleepiness, agitation, difficulty breathing and coma.

To avoid medication errors and the risk of overdose, parents and caretakers are advised that only the syringe provided with the package should be used to measure the dose of Keppra. The different medicine's cartons and labels will be colored differently and clearly indicate the volume of the bottle, the volume of the dosing syringe, and the age range of the child that the medicine should be used for:

The package leaflet will also include clearer instructions for parents and caretakers in order to minimize the risk of using an incorrect dose. Parents and caretakers are advised always to discard the syringe once the medicine's bottle is empty.

The outer packaging and bottle labels of Keppra 100 mg/ml oral solution will use colors to better differentiate each presentation: blue for the 150-ml bottle with 1-ml syringe; green for the 150-ml bottle with 3-ml syringe; and orange for the 300-ml bottle with 10-ml syringe.

Health care professionals should follow these recommendations:

- Doctors should ensure that the age-appropriate presentation of Keppra is prescribed.
- Doctors should always prescribe the dose in milligrams with milliliter equivalence based on the correct age of the patient.
- Pharmacists should ensure that the appropriate presentation of Keppra is dispensed.
- With every prescription, health care professionals should advise the patient and/or caregiver on how to measure the prescribed dose.
- With every prescription, health care professionals should remind patients or caregivers to use only the syringe included in the medicine's package. Once the bottle is empty, the syringe should be discarded.

The cases of overdose with levetiracetam oral solution were reviewed in the context of a safety signal evaluation. A safety signal is information on a new or incompletely documented adverse event that is potentially caused by a medicine and that warrants further investigation.

The review of this safety signal was carried out by the Pharmacovigilance Risk Assessment Committee (PRAC), the Committee responsible for the evaluation of safety issues for human medicines. The PRAC recommendations were sent to the Committee for Medicinal Products for Human Use (CHMP), responsible for questions concerning medicines for human use, which endorsed them. The company that markets Keppra is expected to take action according to the recommendations.

FDA announces mycobacterium chimaera infections associated with LivaNova PLC Stockert 3T Heater-Cooler System

FDA Oct. 13 updated its June 1, 2016, Safety Communication to provide new information about *Mycobacterium chimaera* (*M. chimaera*) infections associated with the use of the Stockert 3T Heater-Cooler System (3T) in U.S. patients who have undergone cardiothoracic surgeries. This communication also contains updated recommendations to help prevent the spread of infection related to the use of these devices.

The device, manufactured by **LivaNova PLC** (formerly **Sorin Group Deutschland GmbH**, is intended to provide temperature-controlled water to oxygenator heat exchangers, cardioplegia (paralysis of the heart) heat exchangers, and/or warming/cooling blankets to warm or cool a patient during cardiopulmonary bypass procedures lasting six hours or less.

Heater-cooler devices are commonly used during cardiothoracic surgeries, as well as other medical

and surgical procedures, to warm or cool a patient in order to optimize medical care and improve patient outcomes. Heater-cooler devices have water tanks that provide temperature-controlled water to external heat exchangers or warming/cooling blankets through closed circuits.

Although the water in the circuits does not come into direct contact with the patient, there is the potential for contaminated water to enter other parts of the device and aerosolize, transmitting bacteria through the air and through the device's exhaust vent into the environment and to the patient.

In October 2015, FDA issued a Safety Communication to provide recommendations to help minimize patient risk of infections associated with heater-cooler devices. Since issuing that communication, FDA has continued to evaluate the causes and risk factors for transmission of microbial agents associated with heater-cooler devices and has collaborated with professional societies, public health partners and experts to develop strategies to minimize patient exposure.

A European study published in April describes a link between M. chimaera clinical samples from several infected cardiothoracic patients in Europe…

A European study published in April 2016 describes a link between *M. chimaera* clinical samples from several infected European cardiothoracic patients, samples from the heater-cooler devices used during these patient's procedures, and environmental samples from the device manufacturer's production and servicing facility in Germany. The results of this paper suggest a direct link between the *M. chimaera* that infected European patients during open-chest cardiac surgery and the *M. chimaera* isolated from the 3T heater-cooler model utilized during these patients' surgeries.

M. chimaera is a type of nontuberculous mycobacterium (NTM) classified as a slow grower. *M. chimaera* may cause serious illness or death. FDA believes *M. chimaera* infections associated with the 3T are rare. However, they are difficult to detect because infected patients may not develop symptoms or signs of infection for months to years after initial exposure.

On June 1, FDA issued a Safety Communication specific to *M. chimaera* infections associated with the use of the 3T. Testing conducted by the manufacturer in August 2014 found *M. chimaera* contamination on the production line and water supply at the 3T manufacturing facility. The 3T devices manufactured at this facility were distributed worldwide. In response to the *M. chimaera* findings in August 2014, the manufacturer added cleaning and disinfection procedures to the production line in September 2014.

Samples taken at the same manufacturing facility by the German Regulatory Authorities in July 2015 did not show *M. chimaera*, potentially indicating the contamination at the manufacturing facility had been resolved. Although the manufacturer of 3T devices added cleaning and disinfection procedures to the production line in September 2014, FDA is now aware of some 3T devices manufactured after September 2014 which have tested positive for *M. chimaera*. It has not been confirmed whether these devices were contaminated at the manufacturing facility or became contaminated at the user facility. To date, FDA is not aware of *M. chimaera* patient infections associated with 3T devices that were manufactured after September 2014.

The June 1 Safety Communication also stated FDA received reports of U.S. patients infected with *M. chimaera* after undergoing cardiothoracic surgery that involved use of the 3T devices. Each of those reports related to 3T devices that were manufactured prior to September 2014.

The Centers for Disease Control and Prevention (CDC) in conjunction with **National Jewish Health** has performed whole genome sequencing on clinical isolates from infected patients and samples taken from the 3T devices from hospitals representing geographically distinct regions within the U.S. (Pennsylvania and Iowa) where clusters of patient infections with *M. chimaera* were identified. Each of the isolates tested were associated with devices manufactured before September 2014.

Samples of the water drained from the 3T devices and air samples collected while the devices were in operation were also tested. The results obtained strongly suggest that the tested 3T devices had a common source of *M. chimaera* contamination.

Sequence comparisons between U.S. and European Union (EU) samples, as well as samples from the manufacturing site, would provide additional information in evaluating the potential for point source contamination at the production site. However, EU sequencing results have not been shared to date.

FDA recommended the health care providers using the device do the following:

- Immediately remove from service any heater-cooler devices, accessories, tubing, and connectors that have tested positive for *M. chimaera* or have been associated with known *M. chimaera* patient infections at your facility.

- Use new accessories, tubing, and connectors to prevent recontamination when using a different heater-cooler device.
- Direct and channel the heater-cooler exhaust away from the patient, e.g., to the operating room exhaust vent.
- Be aware that device contamination also may occur from other sources such as environmental contamination or device contact with contaminated accessories.
- Review the recommendations in CDC's Health Advisory
- Be aware that heater-cooler devices are important in patient care. In appropriately selected patients, the benefits of temperature control during open chest cardiothoracic procedures generally outweigh the risk of infection transmission associated with the use of these devices.

Additional information for patients is available on FDA's Heater-Cooler Devices "Information for Patients" webpage.

FDA also noted that on Dec. 29, 2015, the agency issued a Warning Letter to LivaNova PLC (formerly **Sorin Group Deutschland GmbH**) for its Stockert 3T Heater-Cooler System after inspections conducted at facilities in Munchen, Germany and Arvada, CO, revealed significant issues, including quality system and premarket clearance violations.

Given the serious nature of the violations, the 3T devices manufactured by the Munchen facility are subject to import alert. This restricts the availability of the 3T devices to only those facilities that determine use of the device is medically necessary.

Sorin Group Deutschland GmbH initiated an ongoing corrective action for the 3T in July 2015, and has included updates to instructions for use with new cleaning instructions and instructions for determining if a device is contaminated with biofilm or NTM. Further updates to this recall are expected and will be evaluated by FDA for their ability to further reduce infection risk. Please see FDA medical device recall database entry for more information regarding corrective actions by the manufacturer.

In June 2016, FDA convened the Circulatory System Devices Panel of the Medical Devices Advisory Committee meeting and received expert clinical opinion and recommendations for patient notification and patient follow-up procedures.

The panel also discussed recommendations for sampling and monitoring of the 3T and other heater-cooler devices, including regular visual monitoring of contamination within the water circuit, replacement of accessories (e.g. tubing) on a regular basis, and testing for water quality to assure adequate disinfection procedures are being performed. These recommendations are included in this Safety Communication.

The agency listed the following resources on the device:

- **FDA Communications on Heater-Cooler Devices**
  - Mycobacterium chimaera Infections Associated with Sorin Group Deutschland GmbH Stöckert 3T Heater-Cooler System: FDA Safety Communication (June 1, 2016) - ARCHIVED
  - Nontuberculous Mycobacterium Infections Associated with Heater-Cooler Devices: FDA Safety Communication (Oct. 15, 2015)

  Heater-Cooler Informational Webpage
- **From the Centers for Disease Control and Prevention (CDC)**
  - Perkins KM, Lawsin A, Hasan N, et al. Mycobacterium chimaera Contamination of Heater-Cooler Devices Used in Cardiac Surgery — United States. MMWR Morb Mortal Wkly Rep 2016;65:1117–1118. DOIhttps://emergency.cdc.gov/han/han00397.asp
  - CDC Health Advisory: CDC Advises Hospitals to Alert Patients at Risk from Contaminated Heater-Cooler Devices Used during Cardiac Surgery (Oct. 13, 2016)
  - Interim Guide for the Identification of Possible Cases of Nontuberculous Mycobacterium Infections Associated with Exposure to Heater-Cooler Units (May 13, 2016)
  - Non-tuberculous Mycobacterium (NTM) Infections and Heater-Cooler Devices (Oct. 27, 2015)
- **Medical Literature:**
  - Sommerstein et al. **Transmission of** *Mycobacterium chimaera* **from Heater-Cooler Units during Cardiac Surgery despite an Ultraclean Air Ventilation System.** Emerg Infect Dis. 2016 June;22(6):1008-13.
  - Garvey et al.**Decontamination of heater-cooler units associated with contamination by atypical mycobacteria**. J. Hospital Infection, Volume 93, Issue 3, July 2016:229-34.

FDA warns about risk of hepatitis B reactivating using direct-acting antivirals for hepatitis C

FDA Oct. 4 warned about the risk of hepatitis B virus (HBV) becoming an active infection again in any patient who has a current or previous infection with HBV and is treated with certain direct-acting antiviral (DAA) medicines for hepatitis C virus. In a few cases, HBV reactivation in patients treated with DAA medicines resulted in serious liver problems or death. HBV reactivation usually occurred within four to eight weeks.

As a result, FDA is requiring a Boxed Warning, its most prominent warning, about the risk of HBV reactivation to be added to the drug labels of these DAAs directing health care professionals to screen and monitor for HBV in all patients receiving DAA treatment. This warning will also be included in the patient information leaflet or Medication Guides for these medicines.

Direct-acting antiviral medicines are used to treat chronic hepatitis C virus (HCV) infection, an infection that can last a lifetime. These medicines reduce the amount of HCV in the body by preventing HCV from multiplying, and in most cases, they cure HCV. Without treatment, HCV can lead to serious liver problems including cirrhosis, liver cancer, and death (see List of Direct-Acting Antivirals in the FDA Drug Safety Communication).

FDA identified 24 cases of HBV reactivation reported to FDA and from the published literature in HCV/HBV coinfected patients treated with DAAs during the 31 months from Nov. 22, 2013, to July 18, 2016. This number includes only cases submitted to FDA, so there are likely additional cases about which FDA is unaware. Of the cases reported, two patients died and one required a liver transplant. HBV reactivation was not reported as an adverse event in the clinical trials submitted for the DAA approvals because patients with HBV coinfection were excluded from the trials. See the data summary section in the Drug Safety Communication for more detailed information.

Health care professionals should screen all patients for evidence of current or prior HBV infection before starting treatment with DAAs, and monitor patients using blood tests for HBV flare-ups or reactivation during treatment and post-treatment follow-up.

Patients should tell their health care professional if they have a history of hepatitis B infection or other liver problems before being treated for hepatitis C. Do not stop taking DAA medicine without first talking to health care professionals. Stopping treatment early could result in a virus becoming less responsive to certain hepatitis C medicines.

FDA urged patients to read the patient information leaflet or Medication Guide that comes with each new prescription because the information may have changed, and to contact their health care professional immediately "if you develop fatigue, weakness, loss of appetite, nausea and vomiting, yellow eyes or skin, or light-colored stools, as these may be signs of serious liver problems."

Read the MedWatch safety alert, including a link to the Drug Safety Communication, at:

http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm523690.htm

FDA warns against the use of homeopathic teething tablets and gels

FDA Sept. 30 warned consumers that homeopathic teething tablets and gels may pose a risk to infants and children. FDA recommends that consumers stop using these products and dispose of any in their possession.

Homeopathic teething tablets and gels are distributed by **CVS**, **Hyland's** and possibly others, and are sold in retail stores and online.

Consumers should seek medical care immediately if their child experiences seizures, difficulty breathing, lethargy, excessive sleepiness, muscle weakness, skin flushing, constipation, difficulty urinating or agitation after using homeopathic teething tablets or gels.

"Teething can be managed without prescription or over-the-counter remedies," said Janet Woodcock, M.D., director of FDA's Center for Drugs. "We recommend parents and caregivers not give homeopathic teething tablets and gels to children and seek advice from their health care professional for safe alternatives."

FDA is analyzing adverse events reported to the agency regarding homeopathic teething tablets and gels, including seizures in infants and children who were given these products, since a 2010 safety alert about homeopathic teething tablets. FDA is currently investigating this issue, including testing product samples. The agency will continue to communicate with the public as more information is available.

Homeopathic teething tablets and gels have not been evaluated or approved by FDA for safety or efficacy. The agency is also not aware of any proven health benefit of the products, which are labeled to relieve teething symptoms in children.

J&J warns diabetic patients about hacking risks of insulin pumps

Johnson & Johnson is warning users of its OneTouch Ping insulin pump that hackers could exploit a cybersecurity flaw to infuse additional doses of the diabetes drug without their knowledge, which could be life-threatening, according to an Oct. 4 **Bloomberg News** report.

"The probability of unauthorized access to the OneTouch Ping System is extremely low," the company said in a letter to patients alerting them to the risk. "It would require technical expertise, sophisticated equipment and proximity to the pump, as the OneTouch Ping system is not connected to the Internet or to any external network."

The New Brunswick, NJ-based device maker said it has worked to address the issues and laid out steps patients can take to reduce their risk, such as turning off the pump's wireless connection to a blood sugar meter, or setting a limit on the amount of insulin that can be delivered. While the potential risk with insulin pumps has been known since at least 2011 when a security conference in Las Vegas featured the hack of a **Medtronic** device, the issue has gained attention as more devices include wireless technology to make them easier to use.

A cybersecurity researcher brought the risks to J&J's attention in April after identifying ways to hack the device, according to **Reuters**, which first reported the weakness. That allowed the company to investigate and work with U.S. regulators and the hacker, the same security researcher who earlier exposed the issue with Medtronic's pump.

The experience with J&J's device stands in sharp contrast to the disclosure of similar potential vulnerabilities with **St. Jude Medical's** pacemakers and defibrillators in August. Short-seller Carson Block and his **Muddy Waters Capital LLC** investment firm issued a report with **MedSec LLC**, a cybersecurity company, alleging possible cybersecurity flaws in St. Jude's products. The investment company made a simultaneous short call on St. Jude's shares that allowed it to profit if the stock fell.

Block and his colleagues said they didn't give St. Jude early warning about the potential risks, which has traditionally been the standard in the cyber community, because the deficiencies were so great and St. Jude had been negligent in ignoring them.

St. Jude countered that the deficiencies identified by Muddy Waters and MedSec were actually a safety feature, and that the device the firms tested was functioning normally. **Abbott Laboratories**, which agreed in April to buy St. Jude for $25 billion, has said it remains committed to the transaction.

FDA warns batteries in some St. Jude defibrillators may fail earlier than expected

FDA and **St. Jude Medical** are alerting patients, patient-caregivers and physicians to respond immediately to Elective Replacement Indicator (ERI) alerts, and issue that has led FDA and the company to be involved in the cybersecurity issue involving the devices (see story below).

The company said it would recall some of its 400,000 implanted heart devices due to risk of premature battery depletion, a condition linked to two deaths in Europe, according to Reuters.

Due to problems with these batteries, patients do not have the normal three-month lead time for device replacement. Some batteries have run out within 24 hours of the patient receiving an ERI alert. St. Jude Medical has initiated a recall and correction of the affected devices. See the FDA Safety Communication for a listing of affected devices and data summary.

St. Jude Medical has reported that in some cases, full battery drainage can occur within a day to a few weeks after the patient receives an ERI alert. If the battery runs out, the ICD or CRT-D will be unable to deliver life-saving pacing or shocks, which could lead to patient death. The patients most at risk are those with a

high likelihood of requiring life-saving shocks and those who are pacemaker dependent.

Battery depletion may not always be reported to the manufacturer; therefore, the true number of devices with premature battery depletion due to lithium clusters is not known. At this time, 349,852 affected devices remain actively implanted worldwide.

FDA will continue to monitor affected St. Jude Medical ICD and CRT-D devices for any adverse events related to premature battery depletion or cybersecurity vulnerabilities, and the agency will keep the public informed as new information becomes available.

Implanted defibrillators (ICDs and CRT-Ds) are powered by lithium-based batteries. Deposits of lithium, known as "lithium clusters," can form within the battery and create a billion ormal electrical connections leading to rapid battery failure.

See the FDA Safety Communication for a complete listing of recommendations for health care providers and patients. For health care professionals:

- Do not implant unused affected devices. Premature battery depletion due to lithium clusters has only been observed in devices manufactured prior to May 2015. At this time, there is no information indicating that this issue affects devices manufactured after this date.
- Communicate with all patients who have an affected device that their device has a battery that may run out earlier than expected. Consider giving patients the Dear Patient letter provided by St. Jude Medical.
- Continue to conduct follow-up on patients with affected devices using in-office visits in addition to remote monitoring once they have been notified of the battery issue. Increased in-office surveillance is not necessary for patients who are also followed with remote monitoring.
- Immediately replace the device at the time of an ERI alert. Currently, there is not a factor, method or test to identify when devices with this form of premature battery depletion are approaching ERI, or to accurately predict remaining battery life once ERI appears.
- Pacemaker-dependent patients with a device that has reached ERI should be treated as a medical emergency.
- Health care providers should consider whether elective device replacement is warranted for their pacemaker dependent patients. Ultimately, health care providers should individualize the care of their patients based on the patients' medical history, comorbidities and condition.
- Most patients will not require prophylactic device replacement prior to ERI, as the rate of complications following replacement surgery are higher than those associated with premature battery depletion. However, FDA and St. Jude Medical recognize the need to weigh individual clinical considerations. If the decision is made to replace an affected device based on individual patient circumstances, St. Jude Medical has announced they will provide a replacement device at no cost.
- Enroll patients in Merlin@Home, St. Jude Medical's home monitoring system for these devices, especially those who have difficulty recognizing their device's ERI alerts. For patients already enrolled in Merlin@Home, explain the importance of ongoing home monitoring. Utilize the "Direct Alerts" feature to provide you with an alert notification when a patient's device has reached ERI. Please see additional information about the Merlin@Home Monitoring System below. If a home monitor is ordered for a patient with an affected device, St. Jude Medical will cover the cost of the home monitor.
- Ensure that the ERI battery alert is ON for all patients. Review the most recent "Programmed Parameters" printout.

Read the MedWatch safety alert at: http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm524706.htm

St. Jude to establish cybersecurity advisory board due to issues with devices; FDA investigates with U.S. Department of Homeland Security

St. Jude Medical said Oct. 17 it planned to set up a medical advisory board focused on cyber-security issues affecting patient care and safety due to issues with its cardiovascular devices, **Reuters** reported.

In a subsequent FDA announcement about the recall of the ICDs, FDA said it "recommends that patients, patient caregivers and health care providers enroll in and utilize the St. Jude Medical Merlin@Home monitoring system to help detect battery depletion. FDA is investigating cybersecurity concerns associated with these devices, including the Merlin@Home."

The agency added:

"FDA (in partnership with the Department of Homeland Security ICS-CERT) continues to investigate recent allegations of cybersecurity vulnerabilities associated with St. Jude Medical cardiac devices, including the Merlin@Home monitoring system. Despite the allegations, at this time, FDA strongly recommends that the Merlin@Home device be used to monitor the battery for these affected devices. The ICD and CRT-D devices identified in this safety communication provide life-saving therapy, and FDA believes that the benefits of monitoring outweigh any potential cybersecurity vulnerabilities."

FDA launched that probe in August after short-seller **Muddy Waters** and cyber research firm **MedSec Holdings** said they had placed bets that St. Jude shares would fall after they discovered the alleged vulnerabilities.

St. Jude said in a statement that the group, known as the **Cyber Security Medical Advisory Board**, would provide advice on cyber security standards for medical devices.

"We take the cyber security of our devices very seriously and creating the Cyber Security Medical Advisory Board is one more demonstration of our ongoing commitment to advancing standards of patient care around the world without comprising safety and security," St. Jude Chief Medical Officer Mark Carlson said in a statement.

The board, whose membership has yet to be finalized, will work with technology experts at St. Jude Medical as well as external researchers to help "maintain and enhance cyber security and patient safety," Carlson said.

Suzanne Schwartz, a senior official in FDA's Center for Devices, said the agency supports efforts by medical device manufacturers to prioritize cyber security.

"Doing so in collaboration with other stakeholders such as cyber security researchers, health care providers, patients and government agencies, means cyber security vulnerabilities are more likely to be identified, assessed and fixed in a timely manner before they can cause patient harm," she said in a statement.

Opioids

FDA splits on naloxone dose

A joint meeting of FDA's Anesthetic and Analgesic Drug Products Advisory Committee and Drug Safety and Risk Management Advisory Committee failed to produce consensus on the minimum dose of naloxone needed to reverse the effects of opioid overdose, the **American Pharmacists Assn.** reported in its Oct. 12 newsletter.

A total of 13 members agreed that the current injectable standard of 0.4 mg is effective and should remain in place—many of them expressing concern that raising it could send patients into withdrawal—but 15 argued for a higher minimum dose based on the trend toward abuse of ever more powerful opioids. Voters on both sides agreed, however, that evidence to make an informed decision was lacking.

While the issue of minimum dose remains unresolved, the panelists were somewhat more definitive in a vote on whether to have the same minimum dose for children and adults. In that case, the count was 21-7 to keep those numbers consistent.

Recalls/warnings

McKesson recalls Xanax blister packs with blank labels

McKesson Packaging Services is recalling blister packs of Xanax and a stomach drug because of labeling problems, "FiercePharma" reported Sept. 30.

According to the most recent FDA Enforcement Report, McKesson is recalling 34,920 blister cards because the primary packaging label contains no product information—no product name, strength info, lot number or expiration date. The product was manufactured by Sandoz but packaged by McKesson's North Carolina-based packaging operation and distributed in Colorado, Illinois, Louisiana and Ohio.

Additionally, the company is recalling 1,810 blister packs of the proton pump inhibitor lansoprazole manufactured by **Dr. Reddy's Laboratories** that were shipped nationwide. In that case, the blister packs' outer secondary packaging was mislabeled as 30-mg tablets instead of 40-mg tablets. The inner packaging is properly labeled, the report says.

Both voluntary recalls were issued this month.

The San Francisco-based drug wholesaling giant has been dealing with a variety of issues this year. In January it acknowledged it had eliminated 1,600 jobs, about 4% of its workforce. That announcement came after the company reduced its forecast for the fiscal year as generic pricing pressure and industry consolidation took a toll.

More recently, McKesson's German distributor was raided by Germany's Cartel Office a couple of weeks ago. **Gehe** was one of a number of wholesalers

from which authorities reportedly seized documents as part of a probe into possible price collusion.

Medtronic announces voluntary recall of Pipeline embolization device, Alligator retrieval device, X-celerator hydrophilic guidewire, ultraflow and marathon flow directed micro catheters

Medtronic Oct. 11 announced that it has notified customers of a voluntary recall of certain lots of its Pipeline embolization device, Alligator retrieval device and X-Celerator hydrophilic guidewire. The recall also includes the stylet containing UltraFlow flow-directed microcatheters and Marathon flow-directed microcatheters. These products are produced, marketed and sold by Medtronic's Neurovascular business, which is part of the Brain Therapies division in the company's Restorative Therapies Group.

This voluntary recall is being conducted due to the potential separation and detachment of the polytetrafluoroethylene (PTFE) coating on parts of these devices. Should the PTFE separate from the delivery wire or stylets, PTFE particulate could enter the blood stream of the patient. PTFE in the blood stream, based on the size and quantity, could lead to a thromboembolic event.

Medtronic initiated customer communication of the recall by letter on Oct. 5, 2016, and is requesting customers to quarantine all affected product that remain in the inventory and return to Medtronic. FDA and other regulatory bodies also have been notified, the firm said in its news release.

At the initiation of this recall, 84,278 units potentially affected by this recall had been distributed worldwide. The products were manufactured from July 2014 to September 2016. Additional information about the recall, including the specific lot numbers of affected product, can be found at http://bit.ly/2dTvety.

Medtronic is taking this voluntary action as a precaution and has received no reports of patient injuries to date related to this issue. The full recalled product list of affected lot totals is itemized below:

The Pipeline embolization device is indicated for the endovascular treatment of adults (22 years of age and older) with large or giant wide-necked intracranial aneurysms in the internal carotid artery from the petrous to the superior hypophyseal segments. The first generation Pipeline embolization device is affected by this action due to the PTFE coated delivery wire, which is part of the disposable delivery system (the braid implant is not affected). The second-generation device, Pipeline Flex embolization device, is not affected by this recall.

The Alligator retrieval device is intended for use in the peripheral and neurovasculature for foreign body retrieval. The X-Celerator hydrophilic guidewire is indicated for general intravascular use to aid in the selective placement of catheters in the peripheral, visceral and cerebral vasculature during diagnostic and/or therapeutic procedures.

The UltraFlow flow-directed microcatheter is designed for the subselective infusion of physician-specified therapeutic agents such as embolization materials and diagnostic materials such as contrast media in tortuous, distal vessels. The Marathon flow-directed microcatheter is intended to access peripheral and neurovasculature for the controlled selective infusion of physician-specified therapeutic agents such as embolization materials and of diagnostic materials such as contrast.

Click here to read the full MedWatch/Medtronic announcement: http://www.fda.gov/Safety/Recalls/ucm525582.htm?source=govdelivery&utm_medium=email&utm_source=govdelivery

Leonhard Lang initiates Class I recall of Skintact DF29N Multi-function Defibrillation Electrodes due to connector compatibility issue

The **Leonhard Lang** defibrillation electrode is being recalled due to a connector compatibility issue with the **Welch Allyn** AED model 10. The user may not be able to connect the electrodes to the defibrillator when a shock is needed. This may result in a delay in

delivering the electrical therapy needed to revive a patient in cardiac arrest.

A delay in therapy could result in serious patient injury and/or death.

Recalled product details:

- 50028 Defibrillation Electrode SKINTACT DF29N
- Lot Numbers: 60602-0774, 60502-0779, 60308-0771,60114-0773, 51023-0775, 50904-0777, 50403-0778, 50130-0777, 41023-0771, 41008-0778 40730-0778, 40618-0778, 40130-0776
- Distribution Dates: Feb. 14, 2014, to Aug. 3, 2016

Automatic external defibrillators (AEDs) are used to deliver lifesaving electrical shocks to people with sudden cardiac arrest, a medical condition in which the heart suddenly and unexpectedly stops beating. Defibrillation electrodes are connected to the AED to help the device analyze a patient's heart rhythm and deliver an electrical shock to restore normal heart rhythm when needed.

On Sept. 1, Leonhard Lang sent an "Important Safety Notice" letter to all affected customers. The letter asked customers to:

- Review the safety notice and ensure appropriate staff is aware of the notice.
- Make sure all unused defibrillation electrodes DF29N are secured and destroyed.
- Confirm the products were destroyed by completing the "Confirmation of Destruction / Consumption" form in the notice.
- Send the "Confirmation of Destruction / Consumption" form to their supplier no later than Oct. 14, 2016.
- Keep the signed "Confirmation of Destruction / Consumption" form until their supplier informed them of the termination of this recall.

Health care professionals and consumers with questions are instructed to contact the Leonhard Lang sales staff at (800) 903-6199 with any questions related to this recall.

Read the MedWatch safety alert, including a link to the FDA recall notice, at: http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm525273.htm

Clinical trials

FDA awards 21 grants to stimulate product development for rare diseases

FDA Oct. 17 announced that it has awarded 21 new clinical trial research grants totaling more than $23 million over the next four years to boost the development of products for patients with rare diseases. These new grants were awarded to principal investigators from academia and industry with research spanning domestic and international clinical sites.

"We are proud of our 30-year track record of fostering and encouraging the development of safe and effective therapies for rare diseases through our clinical trials grant program," said Gayatri R. Rao, M.D., J.D., director of FDA's Office of Orphan Product Development, within the Office of Special Medical Programs. "The grants awarded this year will support much-needed research in 21 different rare diseases, many of which have little, or no, available treatment options."

FDA awards the grants through the Orphan Products Clinical Trials Grants Program to encourage clinical development of drugs, biologics, medical devices, or medical foods for use in rare diseases. The grants are intended for clinical studies evaluating the safety and effectiveness of products that could either result in, or substantially contribute to, FDA approval of products.

Since its creation in 1983, the Orphan Products Clinical Trials Grants Program has provided more than $370 million to fund more than 590 new clinical studies and supported the marketing approval of more than 55 products. Five of the studies funded by this grants program supported product approvals in 2015 alone, including much needed treatments for neuroblastoma, lymphangioleiomyomatosis, hypoparathyroidism, and hypophosphatasia.

Consistent with the tenor set by Vice President Joe Biden's National Cancer Moonshot Initiative to accelerate cancer research, 24% of the new grant awards fund studies enrolling patients with cancer and 40% of these studies target devastating forms of brain cancer, one of which recruits children with recurrent or progressive malignant brain tumors.

The agency added that 43% of this year's awards fund studies that enroll pediatric patients as young as

newborns. Of these, two focus on research in transplantation and related issues.

In addition, one funded project is a medical device trial to develop a fully implantable neuroprosthesis for grasp, reach, and trunk function in individuals with spinal cord injury with the potential to enable these patients to use their hand, arm, and trunk more independently.

A total of 68 grant applications were received for this fiscal year, with a funding rate of 31% (21/68). The grant recipients for fiscal year 2016 include:

Drugs/Biologics:

- **Chemigen** (Zionsville, IN), Yansheng Du, Phase I Study of CC100 for the Treatment of Amyotrophic Lateral Sclerosis — about $243,000 for one year
- **Chemocentryx** (Mountain View, CA), Petrus Bekker, Phase II Study of CCX168 for the Treatment of Anti-Neutrophil Cytoplasmic Auto-Antibodies Associated Vasculitis — $500,000 for one year
- **Columbia University Health Sciences** (New York, NY), Elizabeth Shane, Phase IIB Study of Denosumab to Prevent Bone Loss in Idiopathic Osteoporosis in Premenopausal Women Treated with Terripatide — about $1.6 million over four years
- **DNATRIX** (Houston, TX), Frank Tufaro, Phase II Study of DNX-2401 for the Treatment of Glioblastoma — $2 million over four years
- **Elorac** (Vernon Hills, IL), Scott Phillips, Phase III Study of Naloxone Lotion for the Treatment of Pruritus in Mycosis Fungoides — about $2 million over four years
- **Johns Hopkins University** (Baltimore, MD), Pamela Zeitlin, Phase (I/II Study of Glycerol Phenylbutyrate for the Treatment of Cystic Fibrosis — $750,000 over three years
- **Oncoceutics** (Hummelstown, PA), Wolfgang Oster, Phase I/II Study of ONC201 for the Treatment of Multiple Myeloma — about $1.7 million over four years
- **Oregon Health and Science University** (Portland, OR), Kevin Winthrop, Phase II Study of Clofazimine for the Treatment of Pulmonary Mycobacterium Avium Disease — about $1.8 million over four years
- **Santhera Pharmaceuticals** (Liestal, Switzerland), Thomas Meier, Phase I Study of Omigapil for the Treatment of Congenital Muscular Dystrophy — $246,000 for one year
- **Scioderm** (Durham, NC), Jay Barth, Phase III Study of SD101 for the Treatment of Epidermolysis Bullosa — $500,000 for one year
- **Seattle Children's Research Institute** (Seattle, WA), Leslie Kean, Phase II Study of Abatacept Combined with Calcineurin Inhibition and Methotrexate for Prophylaxis of Graft Vs Host Disease — $99,630 for one year
- **Sloan-Kettering Institute Cancer Research** (New York, NY), Katharine Hsu, Phase I Study of Humanized 3F8 MoAb and NK cells for the Treatment of Neuroblastoma — about $750,000 over three years
- **Taimed Biologics USA Corp** (Irvine, CA), Stanley Lewis, Phase III Study of Ibalizumab for the Treatment of Patients with Multidrug Resistant HIV — $500,000 for one year
- **University of Alabama** (Birmingham, AL), Gregory Friedman, Phase I Study of HSV G207 & Radiation for the Treatment of Pediatric Brain Tumors — about $750,000 over three years
- **University of California, San Diego** (La Jolla, CA), Donald Durden, Phase I Study of PI-3 Kinase/BRD4 Inhibitor SF1126 for the Treatment of Hepatocellular Carcinoma — $750,000 over three years
- **University of Florida** (Gainesville, FL), Peter Stacpoole, Phase III Study of Dichloroacetate for the Treatment of Pyruvate Dehyrugenase Complex Deficiency — about $2 million over four years
- **University of Michigan** (Ann Arbor, MI), Kathleen Stringer, Phase II Study of Inhaled Activase for the Treatment of Acute Plastic Bronchitis — $2 million over four years
- **University of North Carolina Chapel Hill** (Chapel Hill, NC), Matthew Laughon, Phase II Study of Furosemide for the Prevention of Bronchopulmonary Dysplasia in Premature Infants — about $1.4 million over four years
- **Vanderbilt University Medical Center** (Nashville, TN), Cyndya Shibao, Phase II Study of Atomoxetine for the Treatment of Multiple System Atrophy — about $1.6 million over four years
- **Wilson Wolf Manufacturing Corporation** (New Brighton, MN), Sunitha Kakarla, Phase I Study of Viralym-A for the Treatment of Adenovirus Disease — about $750,000 over three years

Medical Devices:

- **Case Western Reserve University** (Cleveland, OH), Kevin Kilgore, Phase II Study of a Networked Neuroprosthesis for Grasp, Reach, and Trunk Function in Cervical Spinal Cord Injury — about $2 million over four years