U.S. FOOD & DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

OFFICE OF COMPLIANCE

2019 ANNUAL REPORT

Shielding patients from poor quality, unsafe and ineffective drugs through proactive compliance strategies and risk-based enforcement actions.

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Director's Message

Donald D. Ashley, J.D.
Director, CDER Office of Compliance

I am pleased to present the 2019 annual report for the Office of Compliance in FDA's Center for Drug Evaluation and Research. The report highlights key initiatives where our office's actions during the year had a direct impact on patient safety. We took important actions to reduce the impact of the opioid crisis, protect patients from poorly compounded drugs, alert patients and health care professionals to nitrosamine-related recalls, shield patients from illegally marketed cannabidiol products, implement the Drug Supply Chain Security Act and enhance risk-based monitoring of clinical trials.

The best way to minimize the risk of potentially harmful medicines reaching U.S. patients is to help prevent violations of FDA regulations before they occur. Consequently, we also focused on proactively promoting compliance through clear communication and collaboration with all stakeholders, including through the publication of regulatory policy documents, regular direct engagement with our stakeholders and the launching of the Compounding Quality Center of Excellence.

We utilized a risk-based approach to take compliance and enforcement actions that have the greatest impact on patient health, including actions to help ensure that potentially harmful medicines do not enter the U.S. drug supply chain. In 2019, we issued 166 warning letters across our compliance programs, obtained seven consent decrees of permanent injunction, oversaw good clinical practice inspections and issued clinical inspection summaries for more than 120 new drug and biologics license applications, issued advisory letters to nine companies fraudulently marketing drugs with unproven claims to treat serious diseases and assisted in preventing and mitigating shortages for 56 different medications. We also worked to enhance the data in the drug registration and listing database.

Our accomplishments in 2019 demonstrate our unwavering commitment to shield patients from poor quality, unsafe and ineffective drugs through proactive compliance strategies and risk-based enforcement actions. I look forward to continuing our mission in 2020.

Donald D. Ashley, J.D.
Director, CDER Office of Compliance

Issued 15 warning letters to companies illegally selling various products containing cannabidiol with unproven claims to treat serious diseases

Issued a joint warning letter with the Federal Trade Commission warning a company marketing unapproved cannabidiol product with unsubstantiated claims to treat teething pain and ear aches in infants, autism, attention-deficit/hyperactivity disorder (ADHD), Parkinson's and Alzheimer's disease

Issued a warning letter to a company marketing unapproved cannabidiol products with unsubstantiated claims to treat cancer, Alzheimer's disease, opioid withdrawal, pain and pet anxiety

Key Compliance Initiatives

We focused on several priorities to fulfill our mission to shield patients from unsafe, ineffective and low-quality medicines throughout 2019. We prioritized these initiatives based on the risk to patient health so we could utilize our resources in the most effective way. While we work on many more activities than are outlined below, these are some of the highlights around illegally marketed CBD products, the opioid crisis, compounded drugs, nitrosamine contamination and the drug supply chain:

Shielded patients from illegally marketed CBD products

We worked with other offices in FDA to issue warning letters to companies illegally selling various products containing cannabidiol and warned consumers of the risk posed by these products. There are specific safety concerns related to CBD products, including potential liver injury, interactions with other drugs, drowsiness, diarrhea and changes in mood. In addition, studies in animals have shown that CBD can interfere with the development and function of testes and sperm, decrease testosterone levels and impair sexual behavior in males.

We remain concerned that consumers may also put off getting important medical care, such as proper diagnosis, treatment and supportive care due to unsubstantiated claims associated with CBD products. For that reason, it's important that consumers talk to a health care professional about treatment options scientifically proven to be effective.

We will continue taking appropriate actions when we believe consumers are put at risk.

Took actions to reduce the impact of the opioid crisis

The opioid crisis is one of the largest and most complex public health emergencies that our nation has ever faced. It remains a top priority for CDER Compliance.

We partnered with the U.S. Drug Enforcement Administration to issue joint warning letters to four online networks, operating a total of 10 websites, illegally marketing unapproved and misbranded opioids, including tramadol, that are potentially dangerous. The warning letters issued to each of the networks request that they immediately stop illegally selling these opioids to American consumers. While FDA partners regularly with DEA, this was the first time the two agencies issued joint warning letters. We also issued warning letters to two operators of websites that illegally market potentially dangerous, unapproved and misbranded opioid medications.

We also hosted the second Online Opioid Summit to continue building upon our successes and finding innovative solutions to protect the American public from opioids that are illegally being offered for sale online. The focus of the summit was collaboration with registries and registrars. Since these entities play a role in the registration of internet domain names, they are a critical part of the solution.

Throughout 2019 we identified products that are illegally marketed to treat opioid addiction or withdrawal symptoms and urged consumers to seek appropriate treatment options:

- FDA takes action against marketer of unapproved products claiming to treat addiction, chronic pain and other serious conditions
- FDA issues warning letter for products illegally marketed for the treatment of health conditions, including opioid withdrawal symptoms

We also worked to protect the opioid supply chain. We issued warning letters to three repackers distributing pharmaceutical ingredients, including opioids, for significant violations of CGMP requirements. Drug repackers distribute bulk active pharmaceutical ingredients (API) to drug manufacturers and pharmacy compounders. The supply chain issues we have found in the API repacking industry pose a real threat to the public health and we called on repackers to address these issues as quickly as possible.

Issued four joint warning letters with the U.S. Drug Enforcement Administration to online networks, operating a total of 10 websites, illegally marketing unapproved and misbranded opioids that are potentially dangerous

Issued warning letters to three repackers distributing pharmaceutical ingredients, including opioids, for significant violations of current good manufacturing practice (CGMP) requirements

Refused or destroyed more than 9,000 violative drugs shipped through international mail under the SUPPORT Act

Issued warning letters to six companies marketing unapproved drugs to treat opioid addiction or withdrawal (in March and November)

Additionally, we issued warning letters to companies selling illegal, unapproved kratom drug products marketed for opioid cessation, pain treatment and other medical uses. We continued to urge consumers not to use kratom products following an FDA laboratory analysis of 30 products that found significant levels of lead and nickel at concentrations that exceed safe exposure for oral daily drug intake.

Lastly, the Substance Use-Disorder Prevention that Promotes Opioid Recovery and Treatment for Patients and Communities Act (SUPPORT Act) gave us new authorities to help prevent unapproved and potentially dangerous drugs from entering the U.S. through international mail facilities (IMFs). Since the law was passed in October 2018, we worked with FDA's Office of Regulatory Affairs (ORA) to identify more than 9,800 products processed through all IMFs as drugs because they contain an ingredient that presents a significant public health concern. Of these, more than 9,000 were refused or destroyed.

Protected patients from poor quality compounded drugs

Launched the Compounding Quality Center of Excellence to improve quality of compounded drugs from outsourcing facilities through collaboration and education

Compounded drugs do not undergo FDA premarket review for safety, effectiveness and quality, and present a greater risk of harm to patients than FDA-approved drugs. To help mitigate these risks, FDA has developed a novel approach to engage outsourcing facilities and help them produce the highest quality drugs. The Compounding Quality Center of Excellence is designed to enhance collaboration with, and provide educational programs for, outsourcing facilities with the goal of improving the overall quality of compounded medicines.

We worked closely with our partners in other FDA offices to take regulatory and enforcement actions targeting compounded drugs with the greatest potential to cause harm, including:

- Conducted 102 inspections
- Issued 19 warning letters advising compounders of significant violations of federal law
- Issued 38 letters referring inspectional findings to state regulatory agencies
- Obtained four consent decrees of permanent injunction for Rainier's Rx Laboratory, Guardian Pharmacy Services, Pharm D Solutions and PharMedium Services in collaboration with the Department of Justice
- Requested AmEx Pharmacy recall its sterile compounded drugs and oversaw 50 additional voluntary recalls by compounders

Additionally, we continued to urge compounders to know their bulks suppliers because compounding from bulk drug substances presents additional risks to patients. We have identified issues over the past several years related to repackers of bulk drug substances API used to compound drugs. It's essential that repackers follow all relevant quality standards to protect patient safety and enhance supply chain transparency, including clearly identifying the original API manufacturer to their customers who purchase the bulk API to make the finished drugs patients rely upon every day. In 2019, we issued warning letters to six repackers and distributors of bulk API and will remain vigilant in our inspections and oversight of the supply chain. We also issued a compounding risk alert concerning bulk glutathione distributed to compounders by Letco Medical.

We worked diligently to further develop the statutorily required lists of bulk substances that compounders and outsourcing facilities can use to compound drugs. In particular, for the first time, we placed six bulk drug substances on the 503A bulks list of substances that compounders can use to compound drugs through a final rule. This rule also identifies four bulk drug substances that are not included on the 503A bulks list and therefore cannot be used in compounding under section 503A of the Federal Food, Drug, and Cosmetic Act. The rule, in effect since March 21, also established the criteria for evaluating nominated bulk drug substances for inclusion on the 503A bulks list.

We issued a *federal register* notice identifying nine bulk drug substances the agency considered and is proposing not to include on the 503B bulks list, and a proposed rule amending the 503A bulks list. The proposed rule identifies 26 bulk drug substances the agency has considered and proposes not to include on the 503A list and five bulk drug substances to place on the list.

Helped secure the nation's drug supply chain by implementing the Drug Supply Chain Security Act

The Drug Supply Chain Security Act (DSCSA) outlines steps to enhance FDA's ability to protect consumers from exposure to drugs that may be counterfeit, stolen, intentionally adulterated or otherwise harmful (referred to as "suspect and illegitimate" products under DSCSA) through improved detection and removal of such drugs from the supply chain. We have been working with supply chain stakeholders to implement the law since enactment in 2013 and we reached several significant DSCSA implementation milestones during 2019.

Issued the first warning letter to a wholesale distributor for failing to meet certain DSCSA obligations

We announced the launch of the DSCSA pilot project program. Participants in the program are piloting the use of innovative and

emerging approaches for enhanced tracing and verification of prescription drugs to ensure suspect and illegitimate products do not enter the supply chain. The program is intended to help identify and evaluate the most efficient processes to comply with and apply drug supply chain security requirements. When the program concludes, we will make a final report available to the public so that all supply chain stakeholders can benefit from the information gathered during the pilots.

Additionally, we issued a final guidance for wholesale distributors announcing that the agency does not intend to take action against wholesale distributors who do not, prior to November 27, 2020, verify a product identifier prior to further distributing returned product as required under the DSCSA. This represents a one-year delay in enforcement of this DSCSA requirement.

Alerted patients and health care professionals of nitrosamine-related recalls

Coordinated 41 nitrosamine-related drug recall events, including for ranitidine and angiotensin II receptor blockers

Since mid-2017, the agency has been investigating the detection of nitrosamines in medicines, including angiotensin II receptor blockers (ARBs) and ranitidine. We worked with manufacturers to voluntarily recall medicines when test results showed NDMA above the acceptable daily intake level.

NDMA is a common contaminant found in water and foods including cured and grilled meats, dairy products and vegetables. FDA and the international scientific community do not expect it to cause harm when ingested at low levels. Genotoxic substances such as NDMA may increase the risk of cancer if people are exposed to them above acceptable levels and over long periods of time, but a person taking a drug that contains NDMA at or below the acceptable daily intake limit every day for 70 years is not expected to have an increased risk of cancer.

We also issued four warning letters to companies manufacturing drugs with nitrosamine impurities and placed one company on import alert to prevent their drugs from legally entering the U.S. market.

Proactively Promoting Compliance

We enhanced our outreach efforts to proactively promote compliance across all sectors of the pharmaceutical industry throughout 2019. In addition to establishing the previously mentioned Compounding Quality Center of Excellence, we also engaged industry and other stakeholders in a variety of ways, including issuing guidance documents, authoring articles in publications, speaking at conferences and hosting listening sessions and workshops.

Collaboration with global regulators and other stakeholders is vital to protecting U.S. patients from harm. Whether investigating contaminated or otherwise unsafe medicines or collaborating with other countries during an inspection, this work is critical to keeping the U.S. drug supply chain safe.

We continue to seek opportunities to collaborate and combine our efforts with industry and other stakeholders and seek to ensure that patients have access to safe, effective and quality medicines.

Improved risk-based monitoring approaches of clinical trials

We hosted a workshop with Duke Margolis Center for Health Policy's conference on Improving the Implementation of Risk-Based Monitoring Approaches of Clinical Investigations. This workshop provided us and other regulators, including European Medicines Agency, with feedback from stakeholders on the challenges, barriers and enablers that might

Stakeholder engagement and outreach:

- Held nearly 160 meetings with stakeholders, including regulatory meetings with industry, listening sessions with various stakeholder associations and trainings
- Presented at more than 90 conferences, including 12 international conferences
- Held five public meetings and workshops

Issued 10 draft and final guidance documents, *Federal Register* notices and rulemaking across compliance programs

be impacting the adoption of risk-based monitoring as well as related opportunities to improve risk-based monitoring implementation. Duke Margolis published a paper summarizing the workshop. Benefits of incorporating risk-based monitoring into clinical research include offering a path to updating clinical trial monitoring practices, improving data quality and integrity, protecting human subjects and making clinical trials more cost-efficient.

Collaborated with Health Canada and UK's Medicine and Healthcare products Regulatory Agency on good clinical practice and pharmacovigilance issue

Issued 60 immediate public notifications regarding fraudulent health products

In this era of globalization, regulators need to increase collaboration to optimize resources and enhance regulatory oversight. We regularly engage MHRA on good clinical practice/bioequivalence issues and in 2019, for the first time, we incorporated Health Canada into these efforts. Additionally, we hosted the first-ever collaboration with Health Canada and MHRA on pharmacovigilance inspections and information sharing.

Cosponsored the annual Parenteral Drug Association (PDA)/FDA Joint Regulatory Conference

We cosponsored the annual PDA/FDA Joint Regulatory Conference. Speakers from FDA and the pharmaceutical industry presented on a multitude of topics to help advance the quality of drugs in the U.S. supply chain.

Hosted a registration and listing workshop for industry stakeholders

We hosted the fourth annual drug registration and listing workshop for stakeholders, along with CDER's Small Business and Industry Assistance (SBIA) team. This workshop provided hands-on assistance to industry and live demonstrations of how to create and submit compliant registration and listing files using CDER Direct, an electronic submission portal. The workshop included tips and techniques for saving time and preventing errors, as well as real-time submission support from our team. Timing of this workshop coincided with the beginning of the annual renewal period for updating drug listings and establishment registration information, which runs from October 1 through December 31.

Risk-Based Regulatory and Enforcement Actions

We employed a risk-based approach to regulatory and enforcement actions to minimize patient exposure to harmful medicines and maintain a secure drug supply chain. We strategically prioritized our actions against companies and products that present the greatest risks to patients. In 2019, we focused on several priorities to fulfill our mission of shielding patients from unsafe, ineffective and poor-quality medicines.

Shielded consumers from poor quality drugs by ensuring CGMP compliance

We issued a warning letter to Greenbrier International Inc., doing business as Dollar Tree, for receiving over-the-counter (OTC) drugs produced by foreign manufacturers found to have serious violations of federal law. The letter outlines multiple violations of current good manufacturing practices at contract manufacturers used to produce Dollar Tree's *Assured Brand* OTC drugs, as well as other drugs sold at Dollar Tree and Family Dollar stores.

We also issued a warning letter to Ningbo Huize Commodity Co., an over-the-counter (OTC) drug manufacturer, for significant current good manufacturing practice (CGMP) violations, including data integrity

Issued 166 warning letters across compliance programs

Obtained seven consent decrees of permanent injunction for Rainier's Rx Laboratory, Guardian Pharmacy Services, Pharm D Solutions, PharMedium Services, J and L Grocery, Basic Reset and Biogenyx and Aegerion Pharmaceuticals (filed in 2017; entered in 2019) in collaboration with the Department of Justice

Good clinical practice: Oversaw inspections and issued a clinical inspection summary (CIS) for more than 120 new drug applications (NDAs) and biologics license applications (BLAs)

Issued nine online advisory letters to companies making fraudulent serious disease claims

Assisted in the prevention and mitigation of drug shortages for 56 different medications by exercising regulatory flexibility in 54 separate instances

Number of drug-related recalls we oversaw:

- Class I: 36 events, totaling 513 drugs
- Class II: 242 events, totaling 1,505 drugs
- Class III: 83 events, totaling 150 drugs

issues. To help assure the quality and safety of the drugs relied upon by the American public, we will continue to focus our efforts on preventing, uncovering and combating data integrity violations.

Shielded patients from potentially dangerous unapproved imported drugs

We also issued a warning letter to CanaRx for facilitating the distribution of potentially dangerous unapproved and misbranded drugs to U.S. consumers. The letter expresses our concerns with the scheme CanaRx uses to contract with public and private entities to provide prescription drug coverage to their employees.

Shielded patients from unsafe homeopathic medicines

Risk is an important driver of FDA's regulatory and enforcement actions for all drug products, including homeopathic drugs. We are committed to taking a risk-based approach to homeopathic drug products, and we'll continue taking appropriate regulatory and enforcement actions when we believe patients are put at risk.

To clarify our policy for marketing homeopathic drugs, we worked with CDER's Office of Regulatory Policy to issue a revised draft guidance. The revised draft guidance details a risk-based enforcement policy prioritizing certain categories of homeopathic products that could pose a higher risk to public health, including products with reported safety concerns, products making serious disease claims, products with particular routes of administration, products for vulnerable populations and products with significant quality issues. We also withdrew Compliance Policy Guide (CPG) 400.400, entitled "Conditions Under Which Homeopathic Drugs May be Marketed," as part of this action. Since the issuance of CPG 400.400 in 1988, FDA has encountered multiple situations in which homeopathic drug products posed a significant risk to patients, even though the products, as labeled, appeared to meet the conditions described in CPG 400.400.

Additionally, in 2019, we issued 15 warning letters to companies who produce homeopathic drug products for significant violations of current good manufacturing practice (CGMP) regulations and various other violations:

- FDA warns manufacturers of products labeled as homeopathic for putting consumers at risk with significant violations of manufacturing quality standards

- FDA warns homeopathic firms for putting patients at risk with significant violations of manufacturing quality standards
- FDA takes action against marketer of unapproved products claiming to treat addiction, chronic pain and other serious conditions

Sought voluntary compliance to stop marketing certain unapproved drugs

Following approval of new drug applications for ascorbic acid injection and cocaine hydrochloride, we secured agreements from all manufacturers to voluntarily cease manufacture and distribution of their unapproved versions of these drugs. We continue to encourage all companies that market unapproved drugs to seek FDA approval.

Enhanced the drug registration and listing database

We announced that we would begin deactivating outdated drug listing records from our database that have not been recently updated or certified, as required by regulation, or that include an establishment with an expired registration. Tens of thousands of drug listing records had not been updated or certified within the year, and therefore were not in compliance with federal regulations, which can slow down surveillance operations for certain FDA programs. Many of these listings are for products that are no longer being marketed in the United States, but for which the manufacturer never updated the listing. Such outdated listings compromise the integrity of the drug registration and listing database and limit our ability to make accurate and timely decisions to protect public health. Drugs with inactivated listing records may not be legally marketed or imported in the U.S.

Proactively kept dangerous medicines from entering the U.S. supply chain

We collaborated with ORA to issue import alerts to prevent drugs from a particular facility from legally entering the U.S. Highlights of our work on import alerts in 2019 include:

- Added 41 facilities to import alert 66-40, which lists manufacturing facilities that, based on an FDA inspection, are not operating in conformity with CGMP requirements;
- Added or updated 80 companies to import alert 66-41, which lists companies and products for which we have sufficient evidence to

Concept of Operations (ConOps) agreement and Generic Drug User Fee Amendments (GDUFA II) commitments:

- We issued 232 facility inspection classification letters for GDUFA and facilities not related to our GDUFA commitments
- We issued six GDUFA-related CGMP declaration letters and 27 declaration letters that were not related to our GDUFA commitments
- ORA and CDER have improved consistency in evaluating inspection observations, inspection classifications and decreased the time to take regulatory or enforcement action. The median time to issue a CGMP warning letter following an inspection was 6.5 months in fiscal year 2019. In fiscal year 2016, prior to ConOps, the median time was 12.2 months

demonstrate that a product appears to be an unapproved new drug; and

- Added 32 facilities to import alert 99-32, which lists companies and their products that appear to be adulterated because the companies have refused to permit FDA to inspect the facility.

We also removed facilities from import alert after an onsite reinspection demonstrates the problems have been remediated and the facility is in compliance with FDA laws. In 2019, we removed:

- Three facilities from import alert 66-40;
- Eight facilities from import alert 66-41;
- One facility from import alert 99-32; and
- One facility from import alert 55-05, which lists companies and their finished drug products and active pharmaceutical ingredients that have been detained without physical examination due to potentially hazardous microbiological contamination.

Looking Ahead

In 2020, we will continue promoting voluntary compliance and taking risk-based compliance and enforcement actions to shield patients from unsafe and poor-quality medicine. We also look forward to continuing work on our key priority initiatives to fulfill our mission.

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