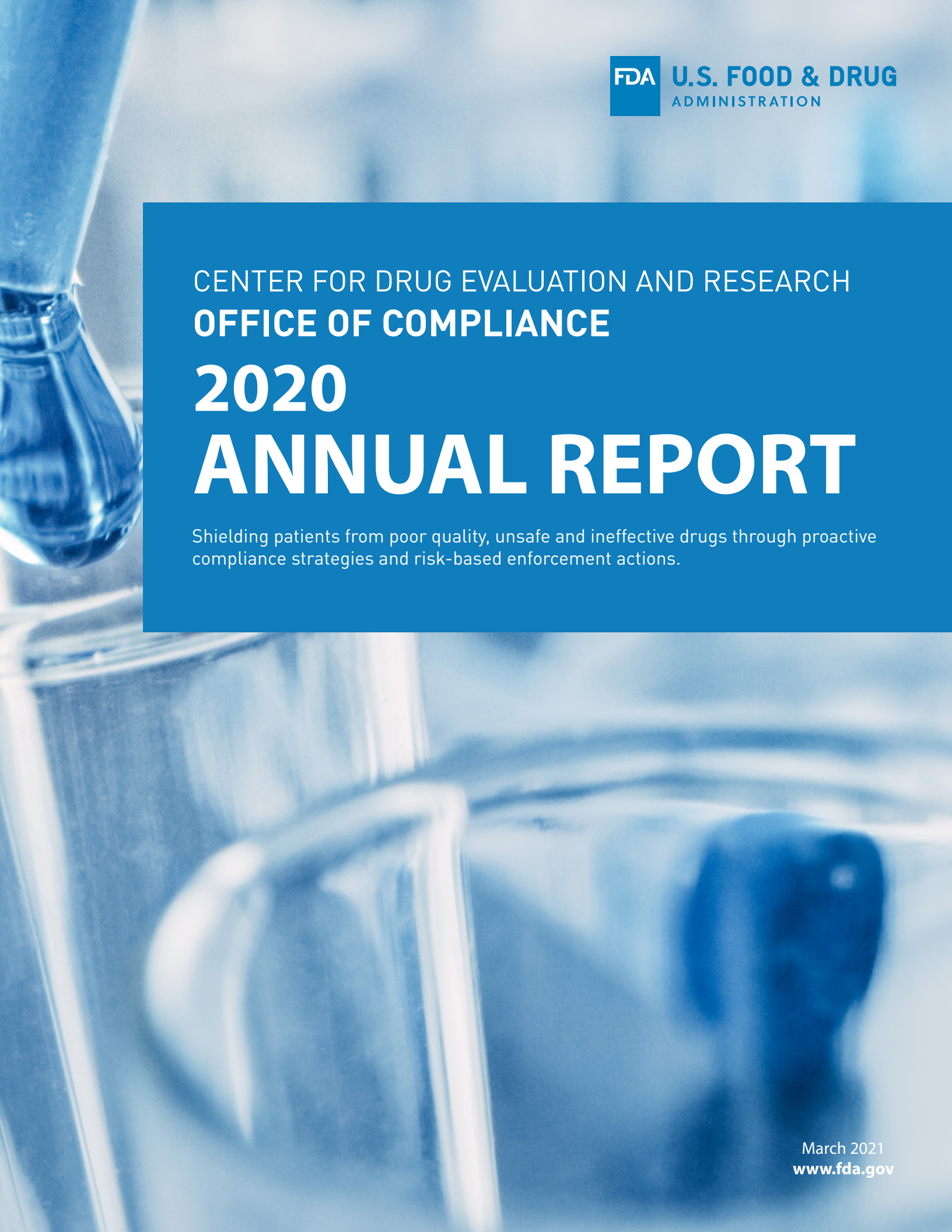

U.S. FOOD & DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

OFFICE OF COMPLIANCE

2020 ANNUAL REPORT

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

March 2021
www.fda.gov

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

Director's Message

I am pleased to present the 2020 annual report for the Office of Compliance in FDA's Center for Drug Evaluation and Research.

This report highlights our key initiatives in 2020 that had a direct impact on patient safety including our efforts to help address the COVID-19 pandemic. We took important actions to help increase access to critical medicines to treat patients with COVID-19, protect consumers from unsafe hand sanitizer products, protect patients from poorly compounded drugs, alert patients and health care professionals to nitrosamine-related recalls and shield patients from unproven products fraudulently claiming to prevent, treat or cure COVID-19.

2020 presented unique challenges around the globe. For those of us who work to shield patients from unsafe, ineffective and poor-quality drugs, this year was especially challenging. However, as an office, CDER Compliance stepped up and worked tirelessly to protect patients.

Even before the public health emergency was declared, we scoured the internet to find products distributed with fraudulent claims to prevent or cure COVID-19. We continue to warn companies, jointly with the Federal Trade Commission, of these violations and tell them to stop distributing these unproven products. We also continue to warn consumers through social media and other tactics not to rely on these fraudulent products.

We became aware of news reports in June of people being harmed from contaminated hand sanitizer, and we swiftly worked to alert consumers not to drink hand sanitizer or use certain hand sanitizers contaminated with methanol and 1-propanol by regularly updating a "do-not-use" list of hand sanitizers on FDA.gov. We have been working with manufacturers to voluntarily recall products, and we continue to encourage retailers to remove violative products from store shelves and online marketplaces. We also listed products that appear violative on import alert to help prevent these products from entering the U.S. supply chain and sent warning letters to many of these manufacturers. Additionally, we warned consumers about hand sanitizers packaged in food and drink containers, such as children's food pouches, water bottles, juice bottles, beer cans and vodka bottles, which may pose a risk of serious injury or death if ingested.

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. The Compounding Quality Center of Excellence is one of our areas of focus in proactively promoting compliance. We were pleased that more than two-thirds of the outsourcing facilities participated in this initiative. The goal of this center of excellence is to improve the quality of compounded drugs. Through our collaboration with outsourcing facilities and other stakeholders, we are uncovering new ways to help compounders implement robust quality management systems that improve patient safety and are better for business.

We use 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 2020, we issued 238 warning letters across our compliance programs, obtained four injunctions, oversaw good clinical practice inspections and issued clinical inspection summaries for more than 114 new drug and biologic applications and assisted in preventing and mitigating shortages for 83 different medications.

Our accomplishments in 2020 demonstrate our unwavering commitment to shield patients from poor quality, unsafe and ineffective drugs. I look forward to continuing our mission in 2021. Stay safe.

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

Advising consumers of hand sanitizer products they should not use

Listing more than 57 manufacturing facilities on a newly created import alert to help prevent further violative products from those manufacturers from entering the United States

Recommending the voluntary recall of more than 170 hand sanitizer products, including six recalls for products with either methanol listed as an ingredient on the product labels, products labeled with "edible alcohol" or packages that resembles food containers

Key Compliance Initiatives

We focused on several priorities to fulfill our mission to shield patients from unsafe, ineffective and poor-quality medicines throughout 2020. With the pandemic as the focal point, we prioritized these initiatives based on the risk to patient health and effective use of our resources. While we work on many more activities than are outlined below, these are some of the highlights of our response to the COVID-19 pandemic and other priority areas such as illegally marketed CBD products, the opioid crisis, compounded drugs, nitrosamine contamination and the drug supply chain.

COVID-19 Response

We issued several guidance documents to provide regulatory flexibility and increase patient access to critical medicines. Additionally, we worked to address contaminated and subpotent hand sanitizers to protect patients.

Shielding consumers from unsafe hand sanitizers

FDA warned consumers and health care professionals the agency had seen a sharp increase in hand sanitizer products that were labeled to contain ethanol (also known as ethyl alcohol) but had tested positive for methanol or 1-propanol contamination. We are also concerned about hand sanitizers labeled to contain methanol as well, as methanol is not an appropriate ingredient in hand sanitizer due to its toxic effects. Methanol, or wood alcohol, is a substance that can be toxic when absorbed through the skin and can be life-threatening when ingested. Children who accidentally ingest hand sanitizer are particularly vulnerable, as are teenagers and adults who ingest hand sanitizer as an alternative source of alcohol.

We published and continue to maintain a "do-not-use" list of hand sanitizers so consumers can check products they have on hand or before they purchase a product.

We warned consumers about hand sanitizer products being packaged in containers that may appear as food or drinks and may put consumers at risk of serious injury or death if ingested. The agency has discovered that some hand sanitizers are being packaged in beer cans, children's food pouches, water bottles, juice bottles and vodka bottles.

We also have found hand sanitizers that contain food flavors, such as chocolate or raspberry. These products could confuse consumers into accidentally ingesting a potentially deadly product. FDA warned manufacturers to be vigilant about packaging and marketing their hand sanitizers in food or drink packages to mitigate potential inadvertent misuse by consumers.

We worked to protect the public from these poor quality and unsafe hand sanitizer products, including those contaminated with methanol or 1-propanol.

JUNE 19 | FDA advised consumers not to use any hand sanitizer manufactured by Eskbiochem SA de CV in Mexico, due to the potential presence of methanol.

JULY 2 | FDA warned that it was aware of adults and children ingesting hand sanitizer products contaminated with methanol that had led to recent adverse events including blindness, hospitalizations and death.

JULY 2 | A new import alert 66-78 was created to include detention without physical examination of drugs when analytical sampling demonstrates a risk for adulteration that pose a health risk due to contamination, substandard quality or ingredient substitution.

JULY 27 | FDA took additional action to help prevent certain hand sanitizers from entering the United States by placing them on an import alert. We proactively worked with manufacturers and distributors to recall all potentially dangerous products from these manufacturers and encouraged retailers to remove products from store shelves and online marketplaces.

JULY 31 | | FDA announced test results that showed certain hand sanitizers have concerningly low levels (subpotent) of ethyl alcohol or isopropyl alcohol, which are active ingredients in hand sanitizer products. We continued to add certain hand sanitizers to import alerts to stop these products from legally entering the U.S. market.

AUGUST 7 | FDA updated guidance documents to provide additional clarification on testing of alcohol used in hand sanitizers manufactured under FDA's temporary policies to help ensure that harmful levels of methanol were not present in these products.

Issuing 14 warning letters to hand sanitizer manufacturers

Successfully collaborating with the U.S. Pharmacopeia to update the monograph for ethyl alcohol to specifically include an identity test for methanol

AUGUST 7 | FDA listed one firm on import alert 66-41 for marketing hand sanitizer products labeled as "edible alcohol."

AUGUST 12 | FDA expanded warnings about certain hand sanitizer products that were labeled to contain ethanol or isopropyl alcohol but had tested positive for 1-propanol contamination.

AUGUST 24 | FDA provided a laboratory testing method to assess the quality of finished hand sanitizer products.

AUGUST 27 | FDA warned about alcohol-based hand sanitizers that were being packaged in containers that may appear as food or drinks and may put consumers at risk of serious injury or death if ingested.

Proactively monitoring the drug supply chain

During the COVID-19 pandemic, FDA closely monitored the drug supply chain with the expectation that it may be impacted by the COVID-19 outbreak, potentially leading to supply disruptions or shortages of drugs in the U.S. We understood the significant impact that this could have on patient care and did everything within our authority to help prevent and alleviate shortages.

We increased patient access to critically needed medications in shortage during the pandemic by:

- Issuing 45 enforcement discretion decisions to increase supplies of remdesivir, heparin, albuterol, etomidate, midazolam, propofol and many other critically needed medications.
- Issuing temporary enforcement discretion policies via two guidance documents on the compounding of drugs needed to treat hospitalized COVID-19 patients.
- Working with CDER's Office of Pharmaceutical Quality on guidance addressing the repackaging or combining of propofol.
- Issuing a guidance document highlighting flexibility under the Drug Supply Chain Security Act to facilitate the distribution of prescription drugs needed to respond to COVID-19, including drugs to treat symptoms of COVID-19. The exemption and exclusion from certain supply chain security requirements balances the need for effective drug distribution under emergency conditions with protecting consumers from exposure to drugs that may be counterfeit, stolen or otherwise harmful.

- Issuing a guidance document describing the temporary policy on Prescription Drug Marketing Act requirements for the distribution of prescription drug samples.
- Issuing a guidance document on the use of non-standard PPE for sterile compounding by pharmacy compounders not registered as outsourcing facilities.
- Working with CDER's Office of Surveillance and Epidemiology on the issuance of guidance for adverse event reporting by outsourcing facilities during a pandemic.
- Working with industry and external stakeholders to complete the required process of registering as a drug manufacturing facility and listing hand sanitizer products with the agency before marketing products to consumers.

Protecting consumers against unproven drugs with fraudulent claims to prevent or treat COVID-19

Unfortunately during emergency situations or outbreaks, unproven products with fraudulent claims to prevent, treat or cure conditions associated with the emergency or outbreak appear for sale. Early in 2020 we began monitoring for unproven products sold with fraudulent claims related to COVID-19 and other conditions, and we have continued to tell companies to cease the sale of such products. We also warned consumers to beware of unapproved and unauthorized products being sold with fraudulent claims to prevent or treat COVID-19, and asked them to report them to the agency. Additionally, we increased our enforcement at ports of entry to ensure that fraudulent products did not enter the country through our borders.

Issued 99 warning letters to companies and individuals selling unproven products with fraudulent claims to prevent or treat COVID-19. More than 85 percent of the recipients took voluntary action in response to these warning letters. Additionally, we issued 11 more warning letters to internet pharmacies selling unapproved medications claiming to treat COVID-19.

Worked with the Department of Justice and FDA Office of the Chief Counsel to successfully obtain injunctive relief against two companies that did not take appropriate action.

Shielding Patients

Although compounded drugs can serve an important medical need for certain patients, they also can present a risk to patients

Protecting patients from poor quality compounded drugs

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 high quality drugs. The Compounding Quality Center of Excellence, launched in 2019, is designed to enhance collaboration with and provide educational programs for outsourcing facilities. Its goal is to improve the overall quality of compounded medicines.

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

As part of this initiative, we hosted in-person, virtual and online current good manufacturing practice and compounding policy trainings for outsourcing facilities. Our inaugural Compounding Quality Center of Excellence virtual conference brought together more than 350 current and future outsourcing facilities, regulators and other compounding experts and stakeholders. Protecting patients from poor quality compounded drugs is a shared responsibility among FDA, states, compounders and other stakeholders. When there's a steadfast commitment to quality vigilance, everyone wins.

An important part of our efforts to improve the overall quality of compounded drugs is to reduce and eliminate insanitary conditions in compounding facilities. We issued an important final guidance document addressing insanitary conditions. This guidance provides examples of insanitary conditions that we've observed during our inspections of compounding facilities and details corrective actions that facilities should take when they identify these

conditions. While some compounders work hard to meet quality standards, FDA investigators too often continue to observe poor conditions that impact drug quality and have the potential to harm patients who use the drugs. These include dirt, mold, insects, trash, peeling paint, unclean exhaust vents and dirty high-efficiency particulate air (HEPA) filters. Our guidance serves as a valuable resource for compounders to better understand insanitary conditions and take necessary actions to avoid such issues for the safety of the patients who receive their drugs. Along with the guidance, we shared our perspectives to help crystalize our concerns in a CDER conversation.

We also worked with CDER's Office of Pharmaceutical Quality to issue a revised draft guidance on current good manufacturing practices (CGMP) for outsourcing facilities. This revised draft was based on feedback from stakeholders on the initial draft guidance to reflect further consideration of how CGMP requirements should be applied based on the size and scope of an outsourcing facility's operations.

We announced the standard memorandum of understanding (MOU) between states and FDA that addresses distribution of compounded drugs and reporting of complaints related to compounded drugs. The availability of the MOU for signature by the states will help enhance communication and maximize federal and state resources for oversight of compounded drugs produced by traditional compounding pharmacies. These partnerships between states that enter into the MOU and the FDA will further our combined efforts to protect the public health. The MOU furthers state regulators' commitment to investigate complaints about adverse drug experiences and product quality issues involving drugs compounded at pharmacies within their state and distributed outside their state.

As an important step in creating the list of bulk drug substances that may be used by outsourcing facilities to compound drugs, we proposed adding four bulk drug substances to the list: diphenylcyclopropenone (DPCP), glycolic acid, squaric acid dibutyl ester (SADBE) and trichloroacetic acid (TCA). We also identified 19 bulk drug substances that we considered and propose not to include on the list. This is a milestone for the compounding program as this is the first time we are proposing to include bulk drug substances on the 503B bulks list.

To alert health care professionals of the risks associated with compounded drugs, we issued a compounding risk alert regarding the intraocular administration of moxifloxacin drugs that contain more than 0.3 mL of 0.5% moxifloxacin or that contain certain potentially harmful inactive ingredients, such as xanthan gum. Additionally, we cautioned health care professionals to carefully consider the concentration and inactive ingredients of any moxifloxacin drug before intraocular administration.

Issued six warning letters to companies illegally selling various products containing cannabidiol (CBD) with unproven claims to treat serious diseases

We also launched the outsourcing facility product reporting database. Our external stakeholders rely on this reporting for critical product information submitted by outsourcing facilities. The improved, searchable database contains two years' worth of data available for public viewing and downloading. The new system also allows for searching by drug name and company name.

Shielding patients from illegally marketed CBD products

We warned two companies illegally selling CDB products with claims that they can treat medical conditions, including opioid addiction or as an alternative to opioids. CBD has not been shown to treat opioid addiction. Opioid addiction is a serious problem in our country, and those who are addicted need to seek out proper treatment from a health care provider.

We also worked with other offices in FDA to issue warning letters to companies illegally selling various products containing CBD 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, consumers should 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.

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.

Reducing the impact of the opioid crisis

Unapproved and misbranded opioids may pose heightened dangers to consumers who purchase those products over the internet. Unlike drugs approved by the FDA, unapproved products have not undergone FDA evaluation to determine whether they are safe and effective for their intended use, or whether they have other safety concerns.

We issued warning letters to 17 website operators for illegally selling unapproved and misbranded opioids online, including products such as tramadol and oxycodone. These warning letters are a continuation of the FDA's commitment to take appropriate action regarding the illegal sale of opioids over the internet.

Additionally, we completed a 120-day pilot with the National Telecommunications and Information Administration to help reduce the availability of unapproved opioids illegally offered for sale online. Under the pilot, the FDA notified participating internet registries when the agency sent a warning letter to a

website operator and the website operator does not voluntarily take appropriate corrective action within the requested timeframe. The internet registries reviewed the FDA's notifications and assessed whether to take further voluntary action, including possible domain name suspensions or blocks.

Helping to 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 2020.

We published our compliance policies in a final guidance document which addresses the readiness of wholesale distributors and dispensers to comply with DSCSA requirements to verify the product identifier on products. The compliance policies provide three additional years for wholesale distributors and dispensers to focus resources and efforts on the requirements for the enhanced drug distribution security system required by November 27, 2023.

We hosted a virtual public meeting on DSCSA implementation, bringing together more than 250 members of the pharmaceutical distribution supply chain and other interested stakeholders to discuss strategies and issues related to the DSCSA enhanced drug distribution security provisions and the results of FDA's DSCSA pilot project program. We will continue to consider the discussions from the public meeting and additional comments received from stakeholders in the public docket as we develop policy and regulation for implementation of the enhanced drug distribution security requirements.

Implementing the DSCSA supports our goals to:

- Prevent harmful drugs from entering the supply chain
- Detect and identify harmful drugs if they enter the supply chain
- Respond rapidly when harmful drugs are found

Shielding consumers from potentially dangerous products with hidden drug ingredients sold through Amazon, eBay and other retailers

We alerted consumers of 46 tainted weight loss or sexual enhancement products purchased through Amazon and eBay after FDA laboratory testing identified hidden drug ingredients. We urged consumers to avoid these products, which were purchased on Amazon and eBay, due to hidden and potentially dangerous drug ingredients. We also encouraged online marketplaces and other retailers to ensure these products are removed from the market and are not sold on their platforms or in their stores.

Coordinated 21 nitrosamine-related drug recall events

Worked with CDER's Office of Pharmaceutical Quality to publish guidance, "Control of N-Nitrosamine Impurities in Human Drugs," which recommends steps manufacturers of active pharmaceutical ingredients and drug products should take to detect and prevent objectionable levels of nitrosamine impurities in pharmaceutical products. The guidance also describes conditions that may introduce nitrosamine impurities.

Issued two warning letters to manufacturers with poor controls to prevent or reduce nitrosamine and other impurity formation

Alerting patients and health care professionals of nitrosamine-related recalls

Since 2018, the agency has been investigating nitrosamine impurities in drugs such as N-Nitrosodimethylamine (NDMA), N-Nitrosodiethylamine (NDEA), 1-methyl-4-nitrosopiperazine (MNP) and 1-cyclopentyl-4-nitrosopiperazine (CPNP) in medicines, including heartburn drug ranitidine, diabetes drug metformin and tuberculosis drugs rifampin and rifapentine.

Nitrosamines are potentially cancer-causing substances, and the source of nitrosamines can be related to the drug's manufacturing process or its chemical structure or even the conditions in which it is stored or packaged. As foods and drugs are processed in the body, nitrosamines can also be formed. Although nitrosamines may increase the risk of cancer if people are exposed to them above acceptable levels and over long periods of time, a person taking a drug that contains nitrosamines at-or-below the acceptable daily intake limits every day for 70 years is not expected to have an increased risk of cancer.

Proactively Promoting Compliance

We enhanced our outreach efforts to proactively promote compliance across all sectors of the pharmaceutical industry throughout 2020. In addition to establishing the 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.

Cosponsoring 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 engage industry and explore the continuing evolution of innovative

Stakeholder engagement and outreach:

- Held more than 130 meetings with stakeholders, including regulatory meetings with industry, listening sessions with various stakeholder associations and trainings
- Presented at more than 59 conferences, including nine international conferences
- Held two public meetings and workshops

Issued 23 draft and final guidance documents and *Federal Register* notices across compliance programs

manufacturing capabilities and the potential effect on quality, compliance and regulatory lifecycle paradigms.

Hosting a registration and listing workshop for industry stakeholders

We hosted the fifth annual drug registration and listing workshop for stakeholders, along with CDER's Small Business and Industry Assistance 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.

Issued 66 immediate public notifications regarding fraudulent health products

Supporting global collaborations to enhance compliance

Strengthening support of our clinical trial oversight:

- We continued to strengthen our important clinical trial oversight collaborations with foreign regulatory counterparts. We collaborated with the Clinical Trials Transformation Initiative and participated in a two-day Pan-American-focused web conference to learn more about stakeholder experiences with the International Council for Harmonisation (ICH) E6 Good Clinical Practice (GCP) guidelines. We also participated in a web conference on stakeholder engagement on ICH E6 Good Clinical Practice. This free public event focused on stakeholder engagement in the Pan-American region to inform the ICH-E6(R3) Expert Working Group (EWG) discussions about updating the guidelines. An organizing committee including EWG members from Brazil, Canada and the United States guided development of the approach and agenda for this meeting.

- We collaborated with the Medicines and Healthcare products Regulatory Agency on the Good Clinical Practice Symposium to provide regulatory perspectives on the importance of sponsor oversight of clinical sites and laboratories, eSource including electronic health records, protocol deviations including the impact on clinical trials and the challenges in ensuring data quality in novel clinical trial designs.

- Enhancing information sharing and efficiency: The Office of Scientific Investigation evaluated its pilot with the European Medicines Agency (EMA) and Japan's Pharmaceutical and Medical Devices Agency (PMDA), and published the EMA-FDA and PMDA GCP Pilot Collaboration Report. The report highlights an 18-month feasibility pilot among FDA, EMA

and the PMDA to evaluate the timing of good clinical practice (GCP) inspections and exchange information related to GCP issues for common marketing applications among the three agencies.

Enhancing our clinical trial oversight

We supported the agency's publication of the ClinicalTrials.gov civil money penalties guidance, which describes the agency's current thinking regarding assessment of civil money penalties against responsible parties and/or submitters of certain applications and submissions to FDA who violate laws and regulations regarding requirements to submit clinical trial registration and/or results information to the ClinicalTrials.gov data bank and/or certain certifications to FDA.

We also issued 31 pre-notice of noncompliance letters for potential noncompliance with ClinicalTrials.gov registration and reporting requirements. By issuing these letters, we are seeking prompt voluntary compliance, and the vast majority of recipients have either stopped their trials or come into compliance with the requirements. We take appropriate action when violations continue.

Additionally, we contributed to the agency's revising of the clinical investigator compliance program. The compliance program was revised to improve readability, clarity and provide context, address the bioresearch monitoring program (BIMO) updates, including those developed from program alignment and harmonization efforts, and reflect current practices and priorities. Additionally, we supported the agency's efforts to publish the BIMO Technical Conformance Guide, which provides current FDA specifications, recommendations and general considerations for preparing and submitting clinical study-level information, subject-level data line listings by clinical site and a singular summary-level clinical site dataset in electronic format.

Announcing policies under the Safe Importation Action Plan

We contributed to a final rule and final guidance that are part of the Safe Importation Action Plan. The rule and guidance describe two pathways aimed at providing safe, effective and lower-cost drugs to U.S. consumers. The rule implements a provision of federal law that allows importation of certain prescription drugs from Canada under specific conditions and the guidance describes procedures drug manufacturers can follow to facilitate importation of prescription drugs that are FDA-approved, manufactured abroad, authorized for sale in any foreign country and originally intended for sale in that foreign country.

Risk-Based Regulatory and Compliance Actions

Issued 238 warning letters across compliance programs

Obtained three injunctions for Genesis II Church, Xephyr LLC doing business as N-Ergetics and Innovative BioDefense Inc., in collaboration with the Department of Justice

Good clinical practice: Oversaw inspections and issued clinical inspection summaries for more than 114 new drug applications and biologics license applications

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 2020, we focused on several priorities to fulfill our mission of shielding patients from unsafe, ineffective and poor-quality medicines.

Shielding consumers from poor quality drugs by ensuring CGMP compliance

In March 2020, FDA announced that it was temporarily postponing most of its domestic and foreign routine surveillance facility inspections due to the emerging COVID-19 public health emergency. During this period, the agency is employing tools to ensure drug safety in the United States, including evaluating manufacturing facilities' compliance with current good manufacturing practice requirements to continue to meet our mission.

We usually evaluate inspection reports produced after onsite inspections. As inspections were postponed, we turned to authorities provided in section 706 of the FDA Safety and Innovation Act (FDASIA) of 2012 (codified at section 704(a)(4) of the Federal Food, Drug and Cosmetic Act) — a records or other

information request in lieu of or in advance of an inspection. While we used these tools prior to the pandemic, this activity in this space increased dramatically. FDA conducted these assessments for facilities prioritized for a surveillance inspection. As a result, 12 manufacturing facilities were placed on import alert based upon violations discovered during this process. Additionally, as part the Mutual Recognition Agreement between FDA and European Union, we can rely on information from drug inspections conducted within each other's borders, also as a result of FDASIA authority. We used the information from an inspection report from another country to place one manufacturing facility on import alert.

Another way the agency can assess drug quality is through testing samples. FDA tested hand sanitizer products and confirmed contamination, which resulted in 14 warning letters. We also added 57 hand sanitizer manufacturing facilities to import alert in 2020 to help prevent potentially dangerous products from entering the U.S.

Shielding patients from unsafe homeopathic medicines

We are committed to taking a risk-based approach to homeopathic drugs, as we do with all drugs, and we'll continue taking appropriate regulatory and enforcement actions when we believe patients are at risk of harm.

As part of the agency's efforts to protect Americans from potentially harmful products, we issued warning letters to four companies for violating federal law by selling unapproved injectable drugs labeled as homeopathic that can pose serious risks. Many of the drugs identified in our warning letters were labeled to contain potentially toxic ingredients such as nux vomica, belladonna (deadly nightshade), mercury and lead. For example, nux vomica contains strychnine, which is a highly toxic, well-studied poison that is used to kill rodents. We are concerned that these potentially toxic ingredients present additional risks of serious harm when delivered directly into the body, including directly into the bloodstream. One of the companies was also cited in the warning letter for substandard manufacturing practices for sterile drugs.

Shielding patients from dangerous salve products

We collaborated with other offices in FDA to address safety concerns related to black salve products, resulting in warning letters to Oneness Labs and Haloderm Inc. We also published a consumer update article warning consumers about the dangers of black salve. Additionally, our colleagues in the Office of Surveillance and Epidemiology published an article on "Cosmetic Disfigurement from Black Salve" in *Drugs & Therapy Perspectives*.

Issued 31 ClinicalTrials.gov pre-notice of noncompliance letters

Issued four online advisory letters to companies distributing products with fraudulent serious disease claims

Conducted 30 bioresearch monitoring remote regulatory assessments

Assisted in the prevention and mitigation of drug shortages for 83 different medications

Number of drug-related recalls we oversaw:

- Class I: 48 events, totaling 110 drugs
- Class II: 235 events, totaling 828 drugs
- Class III: 78 events, totaling 100 drugs

Issued 45 Certificates of Confidentiality to protect the privacy of human subject research participants

Protecting patients in clinical trials

Part of the FDA's mission is to investigate clinical trials and when warranted take action against violations of federal laws and regulations. The FDA is committed to maintaining science-based standards and takes seriously the quality and integrity of clinical research. As part of our efforts, we issued a warning letter to a clinical investigator for failing to ensure an investigation was conducted according to the investigational plan. While only four subjects were enrolled and three randomized at this site, failure to perform these protocol-required procedures raised significant concerns about the protection of study subjects and the reliability of the data collected at the site.

We also issued a notice of initiation of disqualification proceedings and opportunity to explain letter to a doctor for repeatedly or deliberately submitting false information. The doctor had signed and dated study records that falsely indicated many required study procedures were completed over the course of a two-year period.

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

- We issued 113 facility inspection classification letters for GDUFA facilities and those not related to our GDUFA commitments.
- FDA's Office of Regulatory Affairs 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 6.3 months in fiscal year 2020. In fiscal year 2016, prior to ConOps, the median time was 12.2 months.

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

We collaborated with ORA to issue import alerts to help prevent drugs from a particular facility from legally entering the U.S. Highlights of our work on import alerts in 2020 include:

- Added 34 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 97 companies to import alert 66-41, which lists companies and products for which we have sufficient evidence to demonstrate that a product appears to be an unapproved new drug
- Added 20 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
- Created and added 57 facilities to import alert 66-78, which lists manufacturers of drugs at risk for adulteration based on FDA analytical sample results demonstrating violations of the Federal Food, Drug and Cosmetic Act
- Added one crude heparin manufacturer to import alert 55-03 for CGMP violations

Looking Ahead

In 2021, 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 as well as continuing our efforts to respond to the COVID-19 pandemic.

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