U.S. FOOD & DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF COMPLIANCE

CALENDAR YEAR 2018 ANNUAL REPORT

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

May 2019
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CDER/Office of Compliance
First-Ever Accomplishments

- Used our authority for the first time to issue an administrative detention order for human drugs held under insanitary conditions at a salvaging warehouse facility. The products were later seized by U.S. Marshall Service on behalf of the agency.
- Led the first Online Opioid Summit to start a dialogue among key stakeholders about ways to reduce the availability of illicit opioids online.
- Implemented the first-ever compounding policy priorities plan.
- Hosted the first-ever Good Clinical Practice Workshop in collaboration with UK's Medicines and Healthcare Products Regulatory Agency with more than 3,500 stakeholders from more than 70 countries.
- Developed and implemented the first-ever postmarketing adverse drug experience inspection site selection tool.

CDER Office of Compliance
2018 at a Glance

- Stakeholder engagement and outreach: Conducted nearly **200** conference presentations and meetings with stakeholders, including regulatory meetings with industry and listening sessions with various stakeholder associations.
- Public engagement: Held **three** public meetings related to compounding, supply chain security and the national drug code (NDC).
- Policy documents: Issued **23** final and draft guidance documents, Federal Register notices and rulemaking.
- Drug shortages: Assisted in the prevention and mitigation of drug shortages for **52** drugs by exercising regulatory flexibility in **79** instances.
- Good clinical practice: Oversaw inspections and issued a clinical inspection summary (CIS) for more than **130** new drug applications (NDAs) and biologics license applications (BLAs).
- Angiotensin II receptor blocker (ARB) recalls: Coordinated **24** recall events of valsartan, losartan and irbesartan.
- Generic Drug User Fee Amendments (GDUFA II) commitments: Issued **177** facility classification letters.
- Issued a record number of current good manufacturing practice warning letters: **84**.

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Director's Message

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

I am pleased to present the 2018 annual report for the Office of Compliance in FDA's Center for Drug Evaluation and Research. We strive to shield patients from poor quality, unsafe and ineffective drugs through proactive compliance strategies and risk-based enforcement actions. In 2018, we demonstrated, once again, our exceptional commitment to protecting public health.

We reached several first-ever milestones including issuing FDA's first administrative detention order for human drugs, hosting the first Online Opioid Summit and the first Good Clinical Practice Workshop in collaboration with UK's Medicines and Healthcare Products Regulatory Agency with more than 3,500 stakeholders from 73 countries.

Our senior leadership team also developed the Office of Compliance Strategic Plan for 2018–2022. The plan includes our new mission and vision statements, identifies three strategic areas requiring action and dedicated effort over the next five years and 10 priority initiatives focused on, among other areas, compounding, opioids and the Drug Supply Chain Security Act (DSCSA).

Defining clear, risk-based regulatory policy and expectations is an essential component of promoting voluntary compliance within the compounding industry. We led the implementation of the Commissioner's compounding policy priorities plan which outlined key initiatives related to the compounding provisions of the Federal Food, Drug, and Cosmetic Act and advanced the agency's public health mission. We worked in close coordination with other offices across the agency to publish 13 policy documents as part of this plan and continued to protect patients from unsafe or poor-quality compounded drugs.

Taking concrete steps to reduce the impact of the opioid crisis is one of our highest priorities. In June, we met with internet stakeholders, government entities, academic researchers and advocacy groups to discuss ways to collaboratively take stronger action in combatting the opioid crisis by reducing the availability of illicit opioids online. The Summit helped to spearhead a proactive approach by internet stakeholders to crack down on internet traffic in illicit opioids.

Additionally, we issued 17 warning letters to networks operating approximately 370 websites offering misbranded and unapproved opioids to U.S. patients.

We also reached an important milestone related to our efforts to fully implement and operationalize the Drug Supply Chain Security Act (DSCSA). As of November 27, 2018, manufacturers are required to include unique product identifiers on prescription drug packages and cases. This is a key step toward letting the safe and effective drugs move through the supply chain while keeping the bad drugs out. We inspected a large wholesale distributor for DSCSA compliance, and then issued a warning letter to the wholesaler for violations cited in the inspection in 2019.

This year we also managed widespread recalls of generic versions of the angiotensin II receptor blocker (ARB) medicines found to contain nitrosamine impurities that do not meet the agency's safety standards. ARBs are a class of medicines used to treat high blood pressure and heart failure. Nitrosamine impurities, including N-Nitrosodimethylamine (NDMA) and N-Nitrosodiethylamine (NDEA), are probable human carcinogens. The resulting recalls have been among the largest that we have ever managed. To disseminate this information as efficiently as possible, we also provided regular updates on the ARB recalls for patients and health care providers.

Finally, we published draft and final guidance documents on a range of public health issues, pursued stakeholder engagement through outreach, listening sessions and public meetings and continued implementing the facility evaluation and inspection concept of operations agreement between CDER and the Office of Regulatory Affairs (ORA).

2018 was a banner year for CDER Compliance and the dedication of the professionals who serve in this office is more apparent than ever. I am honored to be a part of this team and I look forward to accomplishing even more in 2019.

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

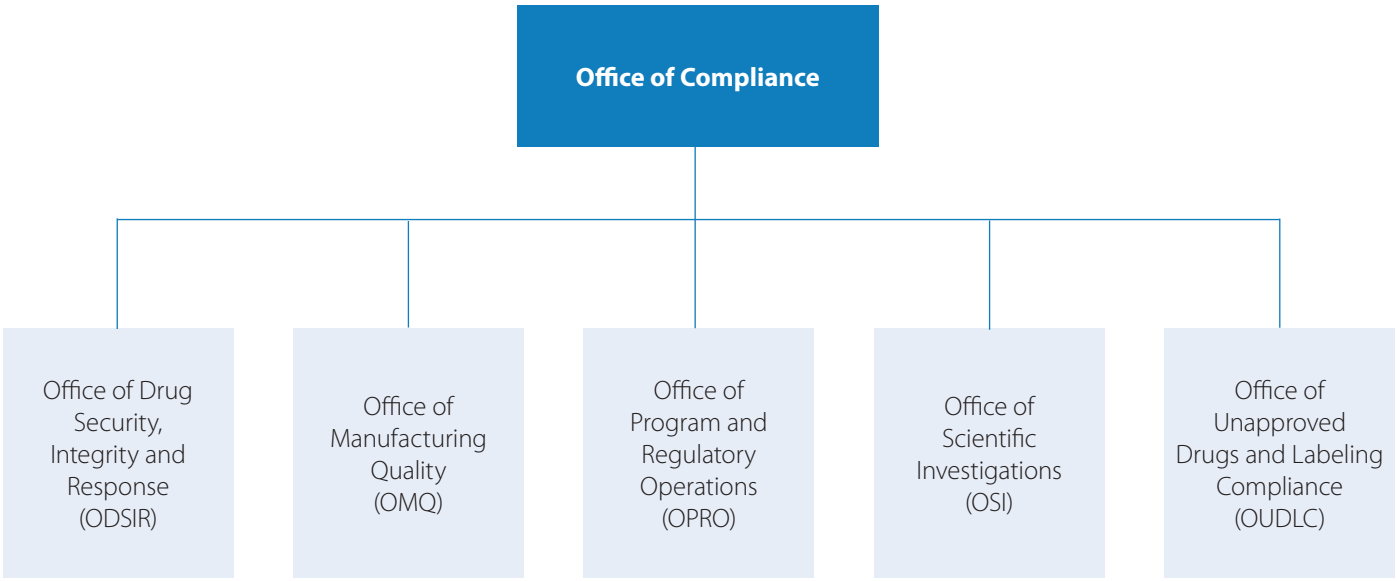
CDER Office of Compliance Overview

Mission: To shield patients from poor quality, unsafe and ineffective drugs through proactive compliance strategies and risk-based enforcement actions.

Vision: To be a model of efficiency, innovation and operational excellence. Guided by law and science, we make strategic and risk-based decisions, communicate clearly with all stakeholders, foster global collaboration, promote voluntary compliance and take decisive action.

CDER Compliance is made up of five component offices that have responsibilities to protect patients throughout the lifecycle of a drug:

- **ODSIR:** Office of Drug Security, Integrity, and Response uses risk-based approaches to promote and protect the integrity of the global supply chain to minimize consumer exposure to unsafe, ineffective, and poor-quality drugs.
- **OMQ:** Office of Manufacturing Quality works to ensure drugs marketed to U.S. consumers are high quality and comply with current good manufacturing practice (CGMP) requirements by



reviewing manufacturing facility inspection findings to determine if drugs consistently meet CGMPs. OMQ develops and implements compliance and enforcement actions to ensure compliance with federal law.

- **OPRO:** Office of Program and Regulatory Operations leads and manages operational infrastructure for CDER Compliance relating to project and process management. OPRO also manages the electronic drug registration and listing database (eDRLS) and works to ensure that information in the database is up to date and accurate.
- **OSI:** Office of Scientific Investigations helps ensure that CDER-regulated drugs, biologics and biosimilars have reliable evidence of safety and effectiveness and meet post-market safety requirements. OSI also protects the rights, safety and welfare of human subjects in clinical trials. In collaboration with the Office of Study Integrity and Surveillance, OSI administers FDA's bioresearch monitoring (BIMO) compliance programs.
- **OUDLC:** Office of Unapproved Drugs and Labeling Compliance oversees drugs that are not approved by the agency, taking regulatory actions and developing policies and compliance strategies to aid in ensuring that over-the-counter and prescription drugs are properly labeled and meet drug approval requirements. OUDLC engages in strategic, risk-based compliance activities to minimize consumer exposure to unsafe, fraudulent and compounded drugs.

Additionally, our Program Management and Analysis Staff (PMAS) is the administrative core of CDER Compliance, providing human resource expertise, budget management, contract management and other key business and operations services that support the office and its employees in protecting public health.

Key Compliance Initiatives

We focused on several priorities to fulfill our mission of shielding Americans from unsafe, ineffective and low-quality medicines. These are some of the highlights:

Taking concrete steps to reduce the impact of the opioid crisis

One of the highest priorities of the agency is to address the opioid misuse and abuse epidemic afflicting the nation. To augment the agency's efforts, we are taking concrete steps to reduce the impact of the opioid crisis, including promoting greater efforts by internet platforms and other companies in the internet ecosystem to reduce the availability of illicit opioids online and by targeting fraudulent opioid addiction treatments for enforcement.

We hosted FDA's first-ever Online Opioid Summit in June. This event gathered academic researchers, advocacy groups, government agencies and leaders of some of the largest internet and technology companies in the country to discuss ways to collaborate and take robust action to reduce the availability of opioids online.

The Summit was a major accomplishment to further FDA's mission to protect public health. We heard presentations on research to better understand how and where these sales are occurring, ways to utilize big data solutions and artificial intelligence, as well as the importance of consumer education to recognize illegal channels. We also discussed ways to connect individuals and families with trusted resources for dealing with substance abuse or addiction.

Since the Summit was announced, internet stakeholders have taken concrete steps to combat the illegal sale of opioids through their platforms and services. For example:

- Google now removes websites from organic search results based on our warning letters that cite the unlawful sale of misbranded and unapproved new drugs to U.S. consumers.
- Social media platforms such as Facebook and Instagram redirect users who are looking to buy opioids online to the Substance Abuse and Mental Health Service Administration National Helpline.

We issued 17 warning letters to networks operating approximately 370 websites offering misbranded and unapproved opioids to U.S. patients.

We also worked with the Federal Trade Commission and the Center for Food Safety and Applied Nutrition to issue joint warning letters to the marketers and distributors of 12 opioid cessation products citing them for illegally marketing unapproved products with claims about their ability to help in the treatment of opioid addiction and withdrawal. Health fraud scams like these can pose serious health risks. These products, and other fraudulent products, have not been reviewed by FDA for safety or effectiveness and may keep some patients from seeking appropriate, FDA-approved therapies. Selling these unapproved products with claims that they can treat opioid addiction and withdrawal is a violation of the Federal Food, Drug, and Cosmetic Act (FD&C Act). We sent warning letters to two companies for marketing homeopathic products to treat opioid addiction and the companies subsequently stopped marketing the products.

Over the past year, the agency has repeatedly warned consumers not to use *Mitragyna speciosa*, commonly known as kratom, a plant which grows naturally in Thailand, Malaysia, Indonesia and Papua New Guinea. In May, we issued warning letters to three companies marketing unapproved kratom-containing products for opioid cessation and other serious diseases. These companies removed the violative claims after receiving our warning letters.

We issued two more warning letters in September to companies for marketing kratom products with claims that were scientifically unsubstantiated. Fraudulent products like these with similar claims may prevent those addicted to opioids from seeking treatments that have been demonstrated to be safe and effective. Reliance on such products may delay their path to recovery and put them at greater risk of addiction, overdose and death. These companies removed the violative claims after receiving our warning letters.

In November, we released information on the risks of heavy metals found in some kratom products. FDA scientists found disturbingly high levels of heavy metals in kratom products. Among the heavy metals we found were lead and nickel at levels not considered safe for human consumption. While the levels of the specific products we've tested so far are not likely to result in immediate acute heavy metal poisoning from a single use, some of these products included levels that, with chronic use, could cause some people to suffer from heavy metal poisoning. We are concerned that there may be other kratom products on the market that also contain heavy metals and we continue to provide public updates to communicate these health risks to patients.

In January, the Commissioner announced a revised and updated Blueprint, "Opioid Analgesic REMS Education Blueprint for Health Care Providers Involved in the Treatment and Monitoring of Patients with Pain," which contains core educational messages for health care providers involved in the treatment and monitoring of patients with pain. It also includes more information on pain management, including the principles of acute and chronic pain management, non-pharmacologic treatments for pain and pharmacologic treatments for pain (both non-opioid analgesic and opioid analgesic). We are working with other offices within CDER to ensure manufacturers are complying with their approved risk evaluation and mitigation strategies (REMS) requirements.

Implementing the compounding policy priorities plan and protecting patient health

Compounded drugs serve an important role for patients whose clinical needs cannot be met by an FDA-approved drug, such as a patient who has an allergy and needs a medication to be made without a certain dye, or an elderly patient or child who cannot swallow a tablet or capsule and needs a medicine in a liquid form that is not otherwise available.

However, compounded drugs are not FDA-approved, which means they have not been reviewed by FDA for safety, effectiveness or quality before they are marketed. Too often we've seen poor compounding practices, such as contamination or medicine that is too potent, that results in patient harm.

"Too often we've seen poor compounding practices, such as contamination or medicine that is too potent, that results in patient harm."

Our ongoing efforts to advance the compounding program and protect patients are focused on two areas:

1. proactively promoting voluntary compliance within the compounding industry; and
2. conducting effective regulatory and enforcement oversight and actions targeting compounded drugs with the greatest potential to cause patient harm.

We worked diligently to implement the compounding policy priorities plan, which was key to our efforts to promote compliance by providing compounders with guidance on policy issues, engaging with stakeholder organizations and collaborating with states on our shared public health goals.

We continue to issue compounding risk alerts to communicate safety concerns and information about adverse events related to the use of compounded drugs. Our goal is to alert health care professionals of these issues so they can more effectively protect patients from unsafe, ineffective and poor quality compounded drugs. We issued or updated four alerts:

- Differences in strength expression on product labels of compounders and conventional manufacturers may lead to dosing errors
- FDA alerts health care professionals of significant safety risks associated with cesium chloride
- FDA's investigation into Guardian's compounded triamcinolone-moxifloxacin drug product

- FDA investigates two adverse events associated with United Pharmacy's compounded glutamine, arginine and carnitine product for injection

To further our collaboration and engagement with our state government partners, we held our seventh annual inter-governmental meeting in September to discuss compounding oversight and DQSA implementation, and to identify opportunities to better protect public health by strengthening oversight of compounders through federal-state collaboration. We also provided training to state pharmacy compliance officers regarding FDA compounding facility inspections. Prior to this meeting, we issued the revised Draft Memorandum of Understanding Addressing Certain Distributions of Compounded Drug Products Between the State of [insert state] and the FDA. The goal of this MOU is to collaborate with the states so that, working together, we can have the greatest public health impact while also maximizing our resources. We revised the MOU to address concerns that were raised by stakeholders to previous drafts of the MOU, while achieving appropriate safeguards for patients.

In July and September we announced our efforts to leverage partnerships with academic medical centers to evaluate evidence related to safety, effectiveness, physical and chemical characteristics and use of compounded drugs, including ingredients being considered for lists of bulk drug substances that can be used in compounding under sections 503A and 503B of the FD&C Act. We are continuing to work with the National Academies of Science, Engineering & Medicine (NASEM), University of Maryland and Johns Hopkins University.

As part of our work to implement the FD&C Act, we issued 13 guidance documents and held one Pharmacy Compounding Advisory Committee meeting.

Examples of oversight activities that FDA conducted include:

	CY 2018
Inspections of compounders	128
Warning letters advising compounders of significant violations of federal law	24
Letters referring inspectional findings to state regulatory agencies	26
Recall events overseen by FDA involving compounded drugs	54
Civil enforcement actions in collaboration with the Department of Justice	2
Voluntary temporary or permanent cessations of operations by compounders	9

Ensuring the most potentially harmful drugs do not enter the U.S. supply chain: Alerting patients and health care professionals of angiotensin II receptor blocker (ARB) recalls

Keeping potentially harmful drugs from reaching patients is a cornerstone of our work, through such actions as recalls and import alerts, among others. When we learned in June that some generic versions of valsartan, an angiotensin II receptor blocker (ARB), contained a probable human carcinogenic impurity — N-Nitrosodimethylamine (NDMA) — that did not meet the agency's standards for safety, we worked to remove these medicines from the market. CDER created a task force of experts from across the center to investigate and coordinate the incident. This team worked to identify the root causes of these impurities and is working with companies to address the risks they pose to patients.

Incident highlights:

- **July**: Three manufacturers — Teva Pharmaceuticals, Solco Healthcare and Major Pharmaceuticals — recalled certain lots of their valsartan-containing medicines made with active pharmaceutical ingredient (API) containing NDMA from Zhejiang Huahai Pharmaceutical (ZHP), Linhai, China.
- **August**: NDMA was found in API manufactured by Hetero Labs, Telangana, India. Camber Pharmaceuticals recalled certain valsartan-containing medicines due to the presence of NDMA. Torrent also recalled certain lots of valsartan-containing medicines because FDA testing confirmed the presence of NDMA in the API made by ZHP. Torrent later expanded its recall to all lots of valsartan-containing medicine.
- **September**: Another probable human carcinogenic impurity — N-Nitrosodiethylamine (NDEA) — was found in valsartan API manufactured by ZHP. Torrent recalled valsartan medicine that contained NDEA. We also placed ZHP's Chuannan facility on import alert to protect patients by stopping all drugs made by ZHP from legally entering the U.S. following an inspection at the facility. Additionally, the agency provided an update on the ongoing investigation.
- **October**: ScieGen recalled certain lots of irbesartan, labeled as Westminster Pharmaceuticals and Golden State Medical Supply Inc. based on testing conducted by FDA which found NDEA. Aurobindo, which manufactured the API for ScieGen's irbesartan medicine, recalled all unexpired lots of its irbesartan API supplied to the U.S. market with NDEA.
- **November**: Sandoz recalled losartan, another medicine in the ARB class, due to NDEA in the API manufactured by ZHP. Teva Pharmaceuticals recalled valsartan-containing medicines manufactured using API from Mylan Pharmaceuticals. Mylan also recalled certain valsartan-containing medicines, which the company later expanded to all lots of valsartan-containing medicine.
- **December**: The agency published interim acceptable daily intake limits of nitrosamine impurities in ARBs for manufacturers to use to ensure their finished drugs are safe for patients. Torrent recalled certain losartan-containing medicines due to NDEA in the API manufactured by Hetero Labs.

Implementing and operationalizing the Drug Supply Chain Security Act requirements

The Drug Supply Chain Security Act (DSCSA) outlines critical steps to build an electronic, interoperable system by 2023 to trace certain prescription drugs distributed in the U.S. The goal of the system is to enhance FDA's ability to protect consumers from exposure to drugs that may be counterfeit, stolen, intentionally adulterated or otherwise harmful 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.

The goal of the [track and trace] system is to enhance FDA's ability to protect consumers from exposure to drugs that may be counterfeit, stolen, intentionally adulterated or otherwise harmful through improved detection and removal of such drugs from the supply chain.

We reached several milestones related to DSCSA implementation. In February, we hosted the third public meeting in a series to further engage stakeholders on strategies for enhanced drug distribution security under the DSCSA. These meetings provided supply chain stakeholders an opportunity to discuss strategies and issues.

In May, we hosted a continuing education course for pharmacists to help explain DSCSA requirements. It is important that pharmacists, or "dispensers" under the DSCSA, know their responsibilities under the law to protect patients from receiving harmful medicine. The DSCSA includes requirements that pharmacies must follow to protect patients from receiving harmful drugs, such as counterfeit or other illegitimate drugs. Additionally, we posted a flyer for pharmacists.

We initiated a for-cause inspection of a wholesale distributor, McKesson Corp., regarding DSCSA requirements for verification, as a result of drug notifications about illegitimate medicines. During the inspection, violations were documented relating to McKesson's practices for record-keeping and investigation of illegitimate medicines.

In November, we reached a key milestone in DSCSA implementation. As of November 27, 2018, manufacturers are now required to include unique product identifiers on prescription drug packages and cases. We created a decision tree graphic to help supply chain stakeholders determine whether the medicine they have can continue to move through the supply chain with or without a product identifier.

In December, we invited representatives from key supply chain stakeholder groups for a listening session to share their top concerns related to DSCSA implementation, and how they envision governance to be organized and function to support enhanced drug distribution security in 2023. This was a useful meeting to help achieve our goal to fully implement and operationalize the DSCSA requirements for licensing of wholesale drug distributors and third-party logistics providers and the enhanced drug security system for 2023.

Additionally, we issued five draft guidance documents and two final guidance documents related to DSCSA implementation.

Fulfilling our GDUFA II commitments

1. **Implementing and operationalizing ConOps by ensuring manufacturers know the classification status following an inspection**

To ensure the agency is meeting its Generic Drug User Fee Amendments (GDUFA II) commitments (which took effect on October 1, 2017), and as part of ConOps (or concept of operations between ORA and CDER), CDER is tracking key performance indicators across the pharmaceutical program. As part of this effort, our efforts are focused on ensuring that manufacturers know, within 90 days of FDA's inspection, whether their facility is in compliance with CGMPs. To carry this out, our specific role was to issue OAI classification letters to facilities within 45 days of receiving the inspection report from ORA. We met this goal 97 percent of the time.

2. **Establishing CGMP declaration letters**

We announced the availability of CGMP declarations in September, which marks another fulfilled commitment under GDUFA II. CGMP declarations are letters to foreign regulators conveying the CGMP compliance status of manufacturing facilities located in the U.S. We committed to issue these letters to foreign regulatory authorities within 30 days of receipt of the request from a facility located in the U.S. when the facility is included as part of an application submitted to a foreign regulator. CGMP declarations are one of several ways that FDA enhances communication and transparency with foreign regulatory authorities regarding the compliance status of establishments in the U.S.

Shielding patients from unsafe drugs

Issuing the first-ever administrative detention order for drugs and seizing food and medical products held under insanitary conditions at an Arkansas grocery warehouse

In November, the U.S. Marshals Service, on behalf of FDA, conducted a mass seizure at J and L Grocery LLC in Alma, Arkansas, of FDA-regulated products that were being held under insanitary conditions in which they were exposed to widespread rodent, insect and live animal infestation. The products seized at the property included human and animal food products, OTC drugs, cosmetic products and medical

devices. A significant number of the OTC drugs were also beyond their stated expiration dates.

The U.S. Department of Justice filed the complaint on behalf of FDA which alleged that an inspection the agency conducted of J and L Grocery in September and October revealed insanitary conditions including multiple live and dead rodents, rodent nesting, live racoons, live cats, a dead possum, animal feces and urine-stained products in and around the company's seven warehouses and sheds used to store food, medical products and cosmetics.

The agency issued two Administrative Detention Orders in October at J and L Grocery, which called for the detention of all human and animal food products as well as drugs. This was the first time we used our administrative detention authority to issue a detention order covering human drugs. During this action, we worked closely with components across FDA, including ORA, Office of the Chief Counsel, CFSAN and the Center for Devices and Radiological Health.

Issuing letters requiring warnings for unapproved prescription local anesthetics

We collaborated with CDER's Office of New Drugs to take action and send letters to manufacturers, repackers, relabelers and distributors of certain OTC and prescription drugs containing local anesthetics, such as benzocaine and lidocaine, requesting that companies take prompt action to relabel these medicines with warnings to help mitigate the risk of methemoglobinemia associated with the use of these medicines. Methemoglobinemia is a potentially fatal blood toxicity associated with the use of local anesthetics.

Alerting consumers, pet owners not to use products manufactured by King Bio

In August, we alerted consumers and pet owners not to use water-based products manufactured by King Bio Inc., Asheville, N.C., due to microbial contamination. The manufacturer expanded its voluntary recall of the products, labeled as Dr. King's, as did several distributors, including:

- Sprayology's voluntary nationwide recall of homeopathic products due to microbial contamination;
- Silver Star Brand's voluntary recall of homeopathic products;
- HelloLife's voluntary recall of products labeled as homeopathic;
- Beaumont Bio Med's voluntary recall of all water- and alcohol-based products; and
- BioLyte Laboratories voluntary recall of NeoRelief

We were concerned about the risk to consumers, especially infants, children, pregnant women and those with compromised immune systems, as well as pets due to high levels of microbial contamination. According to the company, several microbial contaminants were found in its products, including *Burkholderia Multivorans*, which is a strain of bacteria called *Burkholderia cepacia complex* (BCC) that can cause illness or a life-threatening infection in people with compromised immune systems. To protect consumers, we recommended people stop using and dispose of these products immediately. These combined alerts covered more than 900 water-based products.

Reminding consumers to avoid Rhino male enhancement products because of undeclared and potentially dangerous drug ingredients

Over the past few years, FDA has been combatting the retail sale of male enhancement products that are frequently misrepresented as dietary supplements and that contain hidden and potentially harmful active drug ingredients. Distributing unapproved medication, disguised as supplements, places the U.S. public health at risk. In November, we reminded consumers not to purchase or use Rhino male enhancement products, due to a recent rise in reported health issues. Since 2007, the agency has identified more than 25 products marketed with variations of the name "Rhino" that contained hidden drug ingredient(s).

These products continue to be sold (often in single-serving package sizes) at gas stations and convenience stores, as well as on websites such as eBay and Amazon. More recently, these unapproved products have been discovered in international mail shipments to the U.S. Rhino products include names such as Platinum Rhino 25000, Krazzy Rhino 25000 and Gold Rhino 25000.

The agency has received reports of people experiencing chest pain, severe headaches and prolonged erections after taking a Rhino product that led to surgical intervention and hospitalization due to extreme drops in blood pressure.

We previously posted warnings that these Rhino products contain undeclared ingredients found in FDA-approved prescription drugs used to treat erectile dysfunction. For example, we have identified various Rhino products containing sildenafil and/or tadalafil, the active ingredients in FDA-approved prescription drugs Viagra and Cialis, respectively. These undeclared ingredients are phosphodiesterase type-5 (PDE-5) inhibitors, which can be associated with significant safety issues and the risk of serious adverse events. For example, they may interact with nitrates found in some prescription drugs and may lower blood pressure to dangerous levels. People with diabetes, high blood pressure, high cholesterol or heart disease often take nitrates.

Alerting drug makers of a recall of porcine thyroid API from Sichuan Friendly Pharmaceutical Co. Limited, China

We alerted active pharmaceutical ingredient (API) repackagers and distributors, finished drug manufacturers and compounders that Sichuan Friendly Pharmaceutical Co. Limited, China, recalled lots of porcine thyroid API due to inconsistent quality.

FDA laboratory testing confirmed the Sichuan Friendly API had inconsistent levels of the active ingredients levothyroxine and liothyronine, and should not be used to manufacture or compound drugs for patient use. Risks associated with over or under treatment of hypothyroidism could result in permanent or life-threatening adverse health consequences.

This thyroid API comes from porcine (pig) thyroid glands and is used to make a non-FDA approved drug, composed of levothyroxine and liothyronine, to treat hypothyroidism (underactive thyroid).

Additionally, on August 9, Westminster Pharmaceuticals LLC voluntarily recalled all unexpired lots of levothyroxine

and liothyronine (thyroid tablets) 15mg, 30mg, 60mg, 90mg and 120mg. These drugs were made using API from Sichuan Friendly. FDA laboratory testing confirmed inconsistent levels of levothyroxine and liothyronine in the Westminster drugs. Therefore, FDA recommended patients not use porcine thyroid drugs made by Westminster.

FDA placed Sichuan Friendly on import alert 66–40 on March 22 based on CGMP deviations observed during an FDA inspection. We also issued a warning letter on June 22.

Alerting consumers not to use two e-liquids sold by HelloCig Electronic Technology

We worked with the Center for Tobacco Products to issue a warning letter in October to HelloCig Electronic Technology Co. Ltd for various violations of the FD&C Act, including selling two e-liquids that contain the prescription drugs tadalafil and/or sildenafil. Sildenafil and tadalafil are the active pharmaceutical ingredients in FDA-approved prescription drugs used to treat erectile dysfunction. These products were sold illegally since these medicines are not approved for inclusion in e-liquid products sold over the counter. FDA laboratory analysis confirmed "E-Cialis HelloCig E-Liquid" contained undeclared drugs sildenafil and tadalafil, and "E-Rimonabant HelloCig E-Liquid" contained the undeclared drug sildenafil.

We followed up on this warning letter in December with a warning directly to consumers not to purchase or use these two e-liquids sold by HelloCig. We were concerned these undeclared ingredients may interact with nitrates found in some prescription drugs such as nitroglycerin and may lower blood pressure to dangerous levels. People with diabetes, high blood pressure, high cholesterol or heart disease often take nitrates.

Advising health care professionals not to use MedGyn Products' Monsel's Solution

We advised health care professionals in June not to use any Monsel's Solution (ferric subsulfate 20%) because the drug was made under poor conditions. The solution is manufactured by BioDiagnostics International, Brea, California, and distributed by MedGyn Products Inc., Addison, Illinois. Monsel's Solution is used to stop bleeding after medical procedures, such as a colposcopy or a biopsy.

During the agency's inspection of the BioDiagnostics facility, investigators observed insanitary conditions and manufacturing practices which could result in contamination and decreased quality of the Monsel's Solution. While the agency was not aware of adverse events, we warned health care professionals not to use Monsel's Solution to avoid patient harm. We also issued a warning letter to BioDiagnostics on July 12.

Warning of fraudulent and unapproved flu products

As part of our ongoing efforts to protect consumers from health fraud, the agency reminded consumers in March to be wary of unapproved products claiming to prevent, treat or cure influenza. The flu was widespread across the country and we were concerned about the potential for consumers to be lured into buying unproven flu treatments, and even worse, buying counterfeit antivirals online from websites that appear to be legitimate online pharmacies.

Consumers should be aware that there are currently no legally marketed OTC drugs to prevent or cure the flu. However, there are legal OTC products to reduce fever and to relieve muscle aches, congestion and other symptoms typically associated with the flu. Products sold online are fraudulent if they claim to prevent, treat or cure the flu, and have not been evaluated by FDA for that intended use. Health fraud scams waste money, lead to delays in getting a proper diagnosis and treatment and may even lead to more serious injuries or death.

We also reminded consumers that online pharmacies present another opportunity for scammers to take advantage of unsuspecting consumers. Online pharmacies may claim to sell prescription antiviral drugs, such as Tamiflu, at reduced prices with or without a prescription. We advise consumers to avoid purchasing products making such claims, and beware of rogue online pharmacies.

Our BeSafeRx campaign seeks to educate consumers and health care professionals about the health risks of buying prescription medicine through rogue online pharmacies and to help current and potential online pharmacy consumers to make informed purchasing decisions.

Warning consumers that imposters are sending fake warning letters

After hearing from several dozen consumers who received fake warning letters in July, we swiftly alerted the public of this scam. Criminals were forging FDA warning letters to target individuals who tried to purchase medicines online or over the phone. Based on the agency's experience with criminals posing as FDA employees, we were concerned that these fake warning letters were linked to an international extortion scam.

Consumers received official-looking, but fake, warning letters, instead of receiving the drugs consumers attempted to purchase from a website or over the phone. These fake warning letters, purported to be from FDA or FDA and the Federal Trade Commission, and claimed that FDA found drug violations based on a review of the targeted individual's parcel and their social media accounts. The letters are addressed generally to a "Sir/Ma'am," but in some instances may include a specific name. The letters also warn consumers that "we are still investigating the root of this delivery & necessary legal steps will be taken if we found [sic] out any suspicious activity on your end."

We also used this opportunity to remind consumers who buy medicines from illegal online pharmacies that they may be putting their health at risk. The medicines purchased from illegal online pharmacies, while marketed as authentic, may be counterfeit, contaminated, expired or otherwise unsafe.

Rogue online pharmacies may also lack adequate safeguards to protect personal and financial information and some intentionally misuse consumers' information. These websites may infect computers with viruses or sell consumers' personal information to other illegal websites and internet scams. If a consumer buys medicine from an illegal online pharmacy, they also risk being harassed by repeated emails and phone calls or being charged for medicines they never ordered or received.

Proactively Promoting Compliance

We believe the best way to minimize the detrimental impact of potentially harmful medicines is to prevent violations of FDA regulations before they occur. Therefore, we focus on proactively promoting compliance through clear communication and collaboration with all stakeholders. We help facilitate understanding and knowledge of federal laws with a shared goal of achieving voluntary compliance.

We continuously work to enhance our outreach efforts on numerous program areas to proactively promote compliance across all sectors of the pharmaceutical industry. In addition to issuing warning letters and other regulatory actions that we take to alert companies to violations, we engage 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.

In this global pharmaceutical environment, collaboration on a global scale is vital to protecting consumers from harmful medicines. Whether protecting patients from 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 will 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.

Hosting a registration and listing workshop for industry stakeholders

We hosted the second annual registration and listing workshop in October along with CDER's Small Business and Industry Assistance (SBIA) team to provide 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 also 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. We had more than 2,100 attendees in-person and via live webcast.

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

In September, 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.

Determining the future of the national drug code

We held a Part 15 public hearing in November regarding the future format of the national drug code (NDC). The NDC is a unique 10-digit, three-segment identifier which is assigned to all drugs in U.S. commercial distribution. An NDC is proposed by companies and assigned by FDA through the drug listing process. Current formats for the NDC sequence are 4–4–2, 5–4–1 and 5–3–2.

FDA recognizes the importance of the NDC in many aspects of health care today and is aware that any change to its format or length will have an impact on aspects of the health system. Recognizing that a change to NDC length and/or format will be necessary when FDA runs out of five-digit labeler codes, our goal was to receive input from stakeholders on how to maximize the benefit and minimize the impact well in advance of any forthcoming change.

The public hearing served as a listening session that provided stakeholders an opportunity to comment on various NDC formats, proposals for alternate formats and considerations for implementation of new requirements. Additionally, the hearing included presentations from industry and standards setting organizations on the topics of uniformity/standardization of the NDC, considerations for implementation time requirements of the new NDC and potential alternatives to the NDC.

International collaboration: An important component for promoting compliance in the global market

Hosting a regulatory education workshop for industry with MHRA on good clinical practice

To further assist industry in complying with clinical trial requirements, we hosted the first-ever good clinical practice workshop with UK's Medicines and Healthcare Products Regulatory Agency entitled, "Data Integrity in Global Clinical Trials — Are We There Yet?," in October. More than 3,500 external stakeholders from 73 countries registered for this exclusive two-day workshop in October to learn about both regulatory perspectives on the importance of quality management practices on data reliability and take part in several interactive case studies.

Initiating a pharmacovigilance collaboration with UK's Medicines and Healthcare Products Regulatory Agency

We initiated an international collaboration with the United Kingdom's Medicines and Healthcare Products Regulatory Agency (MHRA) focusing on sharing information related to PADE and pharmacovigilance inspections. The goals of this engagement are to increase understanding of each other's pharmacovigilance inspection processes, encourage systematic exchange of inspection information, collaborate on inspections, share information related to best practices and industry trends and optimize the use of limited resources.

Hosting a webinar on postmarketing drug safety and inspection readiness

We hosted a webinar in June entitled, "Postmarketing Drug Safety and Inspection Readiness." The session was developed in collaboration with SBIA. With more than 2,500 registered participants from 68 countries, the webinar provided information on laws regarding Postmarketing Adverse Drug Experience (PADE) and REMS programs, as well as information regarding FDA's inspections.

Joining international working group on PIC/S for good clinical and pharmacovigilance practices

We joined the Pharmaceutical Inspection Co-operation Scheme (PIC/S) working group for Good Clinical Practices and Good Pharmacovigilance Practices. This international working group facilitates technical cooperation and harmonization of practices, including the development of guidance and training material, capacity building and information sharing. Additionally, for the first time ever, FDA participated in the joint visit program in conjunction with the United Kingdom and Canada for the good clinical practice and pharmacovigilance programs. Under this program, each participating country observed inspections in the other two countries to provide training through the exchange of experiences, to provide the means of harmonizing inspection procedures and developing inspection guidance and to ensure and maintain mutual confidence between inspectors of PIC/S participating authorities.

Presenting at International Society for Pharmaceutical Engineering conference in India

In October, we made several presentations at the International Society for Pharmaceutical Engineering (ISPE) conference in Mumbai, India. At this conference, we discussed practical applications of quality systems as part of our efforts to help Indian manufacturers comply with the FD&C Act.

Targeting illegally marketed opioids and other drugs sold online in global operation

In October, we participated in Operation Pangea XI, a global cooperative effort, led by Interpol, to combat the unlawful sale and distribution of illegal and potentially counterfeit medical products sold on the internet. During this operation, we sent seven warning letters to networks that were operating a total of 465 websites illegally selling potentially dangerous, unapproved versions of opioids, oncology and antiviral prescription drugs to U.S. consumers. Additionally, we provided more than 450 illegal domain names to search engines and registrars and registries.

Defining clear risk-based regulatory policy and expectations

Promoting voluntary compliance with FDA regulations necessitates us to provide the pharmaceutical industry information so they have a clear understanding of what standards and expectations are required — and how to comply with them. We play a critical role in the creation of FDA policy. Our goal is to define clear, risk-based regulatory policy and expectations for critical programs under our purview. Improved stakeholder understanding and increased

voluntary compliance will have a direct and substantial impact on the health and welfare of the public. Examples of this work include:

1. **Announcing new policy steps for strengthening public warning and recall notifications**

Our drug recalls team works with companies to take unsafe medicines off the market as quickly and efficiently as possible to shield patients from potential harm. In January, we worked with our recall and policy colleagues across the agency to publish a draft guidance that better describes the agency's policy on public warning and notification of recalled products as part of our effort to ensure better, more timely information reaches consumers.

Specifically, the draft guidance outlines circumstances when a company should issue a public warning about a recall, describes the general timeline for companies to issue such a warning, discusses what information should be included in a public warning and describes situations where we may take action to issue our own public warning should a company's warning be deemed insufficient. The draft guidance also describes the agency's policy for moving forward with posting recalls to FDA's Enforcement Report, which lists all recalls monitored by the agency, before a final health risk determination is made.

The draft guidance is a key step to enhance the recall process. It gives industry clear direction on how to navigate and work with us to make sure recalls are communicated promptly. Ultimately, it will better empower consumers by providing timely and accurate information on recalled products. We are working to finalize this guidance in 2019.

2. **Advancing compliance and enforcement activities to help ensure reliable information on ClinicalTrials.gov**

ClinicalTrials.gov is a data bank managed by the National Institutes of Health/National Library of Medicine, but FDA also plays a role to help ensure the information is accurate. When clinical trial information is properly submitted to ClinicalTrials.gov, patients can more easily seek access to trials and the scientific community can more easily access information that can inform research. The law requires that FDA certify that all requirements have been met by certain applications and submissions for FDA-regulated products. The FDA is responsible for enforcing the clinical trial registration and summary results information submission and certification requirements.

In September we worked with colleagues across the agency to publish a draft guidance on the use of civil money penalties against those who violate the ClinicalTrials.gov requirements, as a way to make sure that we're promoting submission of accurate information that patients and

health care professionals can confidently rely on. The draft guidance outlines how FDA's medical product centers currently intend to identify whether responsible parties have:

- failed to submit required clinical trial registration and/or results information to the ClinicalTrials.gov data bank for clinical trials involving FDA-regulated drug, biological and device products;
- if they have submitted false or misleading information to the data bank; or
- if they have failed to submit or knowingly submitted a false certification to FDA.

The draft guidance also clarifies the circumstances under which FDA may decide to seek civil money penalties for non-compliance, the applicable procedures for assessing civil money penalties and the civil money penalty amounts that may be assessed for violations related to the ClinicalTrials.gov requirements.

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

We collaborate with other offices in FDA to issue import alerts to inform FDA staff and industry that we have evidence of a violation of FDA regulations justifying the detention of a product without physical examination at our borders. Import alerts:

- prevent potentially violative products from being distributed within the U.S.;
- free up agency resources to examine other shipments;
- provide uniform coverage across the country; and
- place the responsibility back on the importer to ensure that the products being imported into the U.S. are in compliance with FDA regulations.

Highlights of our work on import alerts in CY 2018 include:

- Adding 45 facilities to import alert 66–40, which lists manufacturing facilities that, based on an FDA inspection, are not operating in conformity with CGMP requirements;
- Adding or updating 42 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;
- Adding 24 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; and
- Adding one facility to 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.

Guidance documents, rules and regulations published

The following tables outline various types of policy documents we worked to develop:

Draft and Final Guidance Documents Published in CY 2018	
DATE	**LINK**
January 18	Final guidance: Compounded Drug Products That Are Essentially Copies of a Commercially Available Drug Product Under Section 503A of the Federal Food, Drug, and Cosmetic Act
January 18	Final guidance: Compounded Drug Products That Are Essentially Copies of Approved Drug Products Under Section 503B of the Federal Food, Drug, and Cosmetic Act
January 18	Final guidance: Mixing, Diluting, or Repackaging Biological Products Outside the Scope of an Approved Biologics License Application
January 18	Draft guidance: Public Warning and Notification of Recalls Under 21 CFR Part 7, Subpart C *[Office of Regulatory Affairs was the lead on this guidance.]*
February 16	Draft guidance: Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submission
March 2	Draft guidance: Standardization of Data and Documentation Practices for Product Tracing Guidance for Industry
March 2	Draft guidance: Definitions of Suspect Product and Illegitimate Product for Verification Obligations Under the Drug Supply Chain Security Act Guidance for Industry
March 26	Draft guidance: Evaluation of Bulk Drug Substances Nominated for Use in Compounding Under Section 503B of the Federal Food, Drug, and Cosmetic Act
May 9	Draft guidance: Waivers, Exceptions, and Exemptions from the Requirements of Section 582 of the Federal Food, Drug, and Cosmetic Act Guidance for Industry
May 10	Final guidance: Facility Definition Under Section 503B of the Federal Food, Drug, and Cosmetic Act; Guidance for Industry
September 7	Revised draft: Memorandum of Understanding Addressing Certain Distributions of Compounded Drug Products Between the States and the U.S. Food and Drug Administration
September 20	Final guidance: Product Identifier Requirements Under the Drug Supply Chain Security Act — Compliance Policy Guidance for Industry
September 20	Final guidance: Grandfathering Policy for Packages and Homogenous Cases of Product Without a Product Identifier
September 20	Draft guidance: Product Identifiers Under the Drug Supply Chain Security Act — Questions and Answers
September 25	Final guidance: Compounding and Repackaging of Radiopharmaceuticals by Outsourcing Facilities
September 25	Final guidance: Compounding and Repackaging of Radiopharmaceuticals by State-Licensed Nuclear Pharmacies, Federal Facilities, and Certain Other Entities
September 25	Revised draft guidance: Insanitary Conditions at Compounding Facilities
October 25	Draft guidance: Verification Systems Under the Drug Supply Chain Security Act for Certain Prescription Drugs (PDF – 376KB)
December 10	Revised draft guidance: Current Good Manufacturing Practice — Guidance for Human Drug Compounding Outsourcing Facilities *[Office of Pharmaceutical Quality was the lead on this guidance.]*
December 12	Draft guidance: Data Integrity and Compliance With Drug CGMP — Questions and Answers; Guidance for Industry *[Office of Pharmaceutical Quality was the lead on this guidance.]*

Federal Register Notices Published in CY 2018	
DATE	**LINK**
August 7	Public hearing: Future Format of the National Drug Code
August 27	List of Bulk Drug Substances That Can Be Used to Compound Drug Products in Accordance with Section 503B of the Federal Food, Drug, and Cosmetic Act
December 10	Public meeting: The Food and Drug Administration's Proposed Current Good Manufacturing Practice Policies for Outsourcing Facilities: Considerations Regarding Access to Office Stock

Rulemaking Published in CY 2018	
DATE	**LINK**
December 10	Final rule: List of Drug Products That Have Been Withdrawn or Removed From the Market for Reasons of Safety or Effectiveness

Engagement by the Numbers in CY 2018	
Public meetings	3
Regulatory meetings with industry	50
Listening sessions	12
Conference presentations	101
Inter-governmental/50-state meeting	28
External trainings	16
Webinars	1

Number of Safety Notifications for Patients and Health Care Professionals in CY 2018	
Immediate public notifications regarding fraudulent health products	50
Online advisory letters to companies making fraudulent serious disease claims	24
New or updated compounding risk alerts	4

Compliance Actions by the Numbers

Enforcement Actions in CY 2018	
5 PERMANENT INJUNCTIONS OBTAINED	
March 28	Federal judge approves consent decree with Florida company that sold unapproved new drugs and misbranded drugs
April 19	Federal judge enters consent decree against Cantrell Drug Company
June 8	Federal judge enters consent decree against Delta Pharma
August 30	District Court orders permanent injunction against companies selling sexual enhancement products containing undisclosed drugs
October 23	Federal judge enters consent decree against Tennessee over-the-counter drug manufacturer
1 ADDITIONAL PERMANENT INJUNCTION SOUGHT AND STILL PENDING	
June 6	FDA seeks permanent injunction against company selling unapproved hand sanitizers that claim to prevent infections from numerous pathogens
1 SEIZURE	
November 7 and 8	FDA seizes food and medical products held under insanitary conditions at an Arkansas grocery warehouse

Number of Drug-Related Recall Events Overseen by CDER Compliance in CY 2018	
Class I	46
Class II	234
Class III	110

Number of Recalled Drug Products Overseen by CDER Compliance in CY 2018	
Class I	104
Class II	1,155
Class III	147

Additional Enforcement Actions in CY 2018	
Clinical investigator disqualifications	1
Companies and/or products added to import alerts	112

Number of Drug-Related Warning Letters (except advertising violations) in CY 2018	
ODSIR	20
OMQ	84
OPRO	4
OSI	2
OUDLC	32
Total	**142**

Number of Drug-Related CGMP Warning Letters that Included Data Integrity Violations in CY 2018	
Total number of CGMP WLs	**84**
Number of CGMP WLs that included data integrity violations	**30**

Looking Ahead

In 2019, we will continue promoting compliance through clear communication and collaboration with stakeholders, while, at the same time, pursuing effective, risk-based regulatory and enforcement actions to shield patients from unsafe, ineffective and poor-quality medicines. Our focus will include three key areas:

1. The opioid crisis

We will continue to take concrete steps across all our compliance programs to reduce the impact of the opioid crisis. In particular, we will continue our work with internet stakeholders and federal partners to reduce the availability of opioids illegally distributed online. We will also continue our regulatory and enforcement actions aimed at preventing consumer exposure to drugs fraudulently marketed as treating opioid addiction and withdrawal as well as against opioid-like alternative drugs.

2. Improving the quality of compounded medicines

We will continue to balance the need to preserve access to appropriately compounded medicines for patients who have a medical need for those medicines with the need to help shield patients from poor quality compounded medicines that could cause harm. In particular, we will initiate efforts to offer in-depth training for outsourcing facilities on CGMP requirements to improve the quality of compounded medicines. At the same time, we will continue to take regulatory and enforcement actions targeting compounded medicines with the greatest potential to cause patient harm.

3. DSCSA — another year closer to 2023

As we continue our work to implement DSCSA, we envision that this electronic, interoperable track-and-trace system will provide increased public health benefits by creating a tighter, closed system that will prevent the introduction of illegitimate medicines, better detect suspect and illegitimate medicines and enable us and stakeholders to rapidly *respond* when such medicines are found in the drug supply chain.

We recently launched a new pilot project in which participants representing the drug supply chain (e.g., manufacturers, repackagers and other stakeholders) can pilot the use of innovative and emerging approaches for enhanced tracing and verification of prescription drugs in the U.S. to ensure suspect and illegitimate medicines do not enter the supply chain. This new program will pilot technologies and approaches in 2019 that may become part of our enhanced expectations for reliable track-and-trace systems.

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