



U.S. FOOD & DRUG
ADMINISTRATION

FDA'S HUMAN DRUG
**COMPOUNDING
PROGRESS
REPORT**

Three Years After Enactment of the
Drug Quality and Security Act

A photograph of a laboratory setting, showing a glass mortar and pestle, a glass vial, and a brown glass bottle on a white tray.

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**FDA's Human Drug
Compounding Progress Report:**
Three Years After Enactment of the
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Executive Summary

Just over three years ago, on November 27, 2013, Congress amended the Federal Food, Drug, and Cosmetic Act (FD&C Act) by enacting the Drug Quality and Security Act (DQSA). The first title of the DQSA, known as the Compounding Quality Act, was passed in response to numerous serious adverse events, including deaths, linked to poor quality compounded drugs. In particular, in 2012, injectable drug products produced by a compounder and shipped across the country caused a fungal meningitis outbreak that resulted in more than 60 deaths and 750 cases of infection, affecting patients in 20 states.

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Compounded drugs can serve an important medical need for patients. However, if a compounded drug does not meet appropriate quality standards (e.g., if an injectable drug is contaminated, or if a tablet contains too much active ingredient), it could cause serious injury or death. Therefore, in implementing and enforcing the compounding-related provisions of the FD&C Act, FDA seeks to strike a balance between preserving access to lawfully-marketed compounded drugs for patients who have a medical need for them while protecting patients from the risks associated with compounded drugs that are not produced in accordance with the applicable requirements of federal law.

FDA has devoted significant agency resources to implementing and enforcing the compounding-related provisions of the FD&C Act, including those added by the DQSA, in the wake of the 2012 fungal meningitis outbreak and other serious injuries and deaths.

Over the past three years, FDA has:

- Significantly increased its inspections of facilities where drugs are being compounded and taken appropriate regulatory actions in response to violations of the law that put patients at risk;
- Issued numerous policy documents, including draft and final guidance documents and proposed and final regulations;
- Convened advisory committee meetings to obtain advice on scientific, technical, and medical issues concerning drug compounding;
- Obtained input from stakeholders through a variety of different mechanisms; and
- Worked closely with states to share information and coordinate efforts.

FDA's oversight efforts have had a significant public health impact. For example, after FDA inspections and regulatory actions, many compounders have implemented corrective actions to address poor practices that could lead to quality problems, such as drug contamination, that put patients at risk. Others have initiated voluntary recalls of drugs that may have been contaminated or otherwise of poor quality or ceased operations until implementing appropriate corrective actions. FDA's policy development and outreach efforts have also helped to clarify applicable regulatory requirements that are in place to protect the public health. However, much remains to be done.

FDA continues to investigate many reports of serious adverse events associated with contaminated or otherwise poor quality compounded drugs, including sterile and non-sterile drugs that were thousands of times stronger than labeled. FDA also has identified insanitary conditions at the majority of sterile drug compounders that it has inspected since enactment of the DQSA. Insanitary conditions can cause drugs to become contaminated and lead to serious patient injury and death. Examples of recent inspectional observations include dog beds and dog hairs in close proximity to a sterile compounding room, dead insects in ceilings, renovations made without any evidence of controls to protect sterile drugs from contamination, and use of coffee filters to filter particulates.

FDA intends to build on its initial efforts to implement and enforce the compounding provisions of the law in the coming months and years. Maintaining vigorous oversight, continuing to explain regulatory requirements through policy development, and fostering collaboration with states and stakeholders are vital to achieving broader compliance with the provisions of federal law intended to help protect patients.

The Regulatory Framework and History of Drug Compounding Regulation

Most prescription drugs are required to:

- undergo premarket approval to demonstrate safety and efficacy;
- be labeled with adequate directions for use so patients can safely use drugs for their intended purposes; and
- be manufactured according to current good manufacturing practice (CGMP) requirements, which are intended to assure the identity, strength, quality, and purity of drugs by requiring adequate control of manufacturing operations.

These requirements provide important protections to patients. Under certain conditions, however, compounded drug products are not subject to these requirements. Other protections, such as the prohibition on preparing drugs under insanitary conditions, apply to all drug products, including compounded drugs.

What is Drug Compounding?

Drug compounding is often regarded as the process of combining, mixing, or altering ingredients to create a sterile or non-sterile medication tailored to the needs of a patient. Compounded drugs are not FDA-approved.

A drug may be compounded for a patient who cannot be treated with an FDA-approved medication, such as a patient who has an allergy and needs a medication to be made without a certain dye, or an elderly patient or a child who cannot swallow a tablet or capsule and needs a medicine in a liquid dosage form that is not otherwise available. Practitioners in hospitals, clinics, and other health care facilities sometimes administer or dispense compounded drugs to patients when an FDA-approved drug is not medically appropriate to treat them.

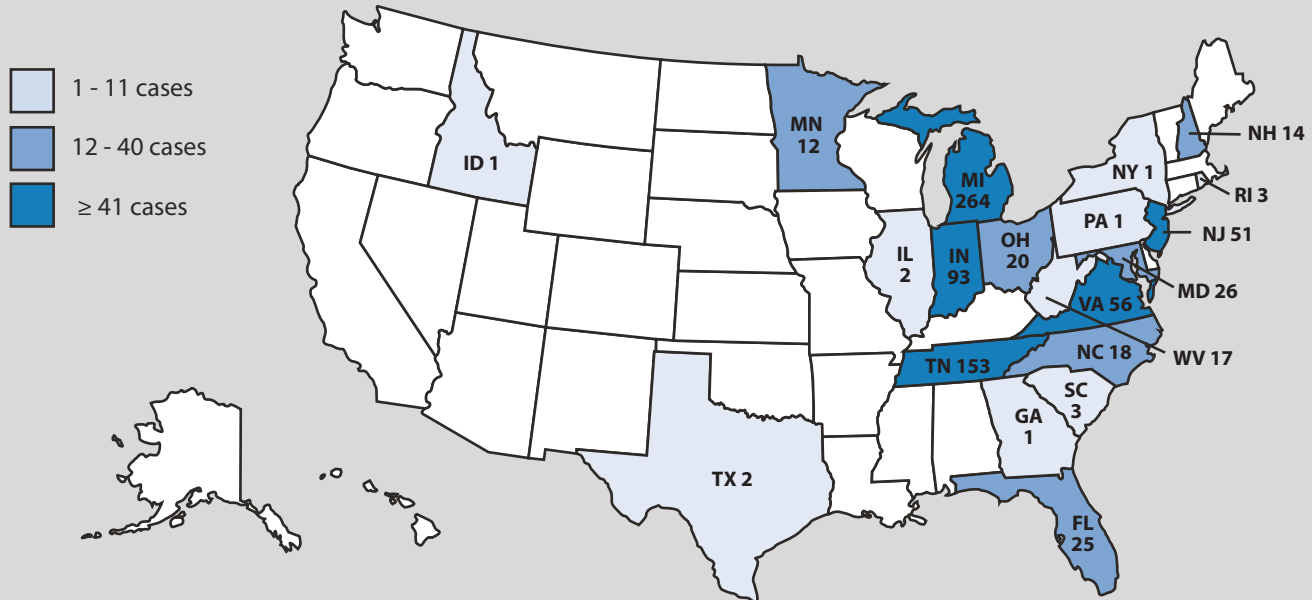
In these situations, compounding can serve an important patient need. However, some compounders engage in inappropriate compounding activities. For example, FDA is aware that some compounders produce drugs for patients even though an FDA-approved drug may have been medically appropriate for them. FDA has also observed that some compounders have advertised compounded drugs as safe and effective, sometimes for the treatment of serious diseases, incorrectly suggesting the drugs had met the standard for FDA approval.

Risks of Compounded Drugs

Because compounded drugs are not FDA-approved, FDA does not verify their safety, effectiveness, or quality before they are marketed. FDA also has observed that the labeling of compounded drugs often omits important information such as directions to help ensure that the drugs are used safely and warnings about possible side effects and drug interactions. In addition, and of particular concern, poor compounding practices can result in serious drug quality problems, such as contamination or medications that do not possess the strength, quality, and purity they are supposed to have. This can lead to serious patient injury and death.

In October 2012, the United States faced the most serious outbreak associated with contaminated compounded drugs in recent history. A pharmacy in Massachusetts shipped contaminated compounded drugs to patients and health care providers throughout the country. The drugs, which were contaminated with fungal growth, were injected into patients' spines and joints. More than 750 people in 20 states developed fungal infections, and more than 60 people died as a result. Approximately 14,000 patients received injections from the lots of contaminated drug product.

2012 Fungal Meningitis Outbreak: Persons with Fungal Infections Linked to Steroid Injections, by State.
[Centers for Disease Control and Prevention](#)



The 2012 fungal meningitis outbreak was not an isolated event. It was the most serious in a long history of serious adverse events associated with contaminated, super-potent, mislabeled, or otherwise poor quality compounded drugs. In addition, many serious adverse events linked to poor quality compounded drugs, including outbreaks of infections and deaths have occurred since then. And, because most compounders do not report adverse events to FDA, the agency may not be aware of adverse events associated with compounded drugs unless a health care provider submits an adverse event report regarding his or her patients or a state official notifies FDA.

To balance the public health need for compounded drugs and the risks such drugs can present to patients, Congress enacted two provisions that provide for human drug compounding without, for example, obtaining FDA approval, but only if certain conditions are met. These two provisions are sections 503A and 503B of the FD&C Act.

Section 503A of the FD&C Act

During the 1990s, there was significant growth in the number of entities compounding drugs, and in particular, entities that were supplying large quantities of compounded drugs to hospitals and other customers nationwide. In 1997, Congress enacted a provision to address the growing sector, codified in section 503A of the FD&C Act.

Under section 503A, drug products that are compounded according to certain conditions are exempt from three requirements of the FD&C Act:

- premarket approval requirements,
- the requirement for labeling with adequate directions for use, and
- CGMP requirements.



“It is the intent of the conferees to ensure continued availability of compounded drug products as a component of individualized therapy, while limiting the scope of compounding so as to prevent manufacturing under the guise of compounding. Section 503A establishes parameters under which compounding is appropriate and lawful”

Joint Explanatory Statement of the Congressional Committee of Conference regarding to the enactment of section 503A in 1997

Among the conditions to qualify for exemptions are that the drug must be compounded by a licensed pharmacist in a state-licensed pharmacy or federal facility, or by a licensed physician, based on the receipt of a valid patient-specific prescription. Other conditions address, for example, the kinds of bulk drug substances that can be used in compounding, and restrictions on the compounding of drugs that are essentially copies of commercially available drug products.

Compounded drugs that meet the conditions of section 503A are still subject to other public health protections in the FD&C Act, such as the prohibition on insanitary conditions. Compounded drugs that do not meet the conditions of section 503A (or the conditions of section 503B, discussed below) are subject to all of the requirements of the FD&C Act applicable to conventional drug manufacturers.

When it was added to the FD&C Act in 1997, section 503A included restrictions on the advertising of compounded drugs. In 2002, the United States Supreme Court struck down these advertising restrictions as unconstitutional but did not address whether they were severable or rendered all of section 503A invalid. The Court’s decision, and conflicting rulings from federal circuit courts, contributed to uncertainty about the applicability of section 503A, and led to disputes about FDA’s authority to regulate compounders.

DQSA and Section 503B of the FD&C Act

On November 27, 2013, a year after the 2012 fungal meningitis outbreak, Congress enacted the Compounding Quality Act of the DQSA to clarify and enhance the public health protections applicable to compounded drug products, and to help prevent a recurrence of tragedies like the 2012 fungal meningitis outbreak and the other serious adverse events and deaths that occurred before then. Specifically, the DQSA removed the advertising provisions from section 503A that had been found to be unconstitutional, which removed uncertainty about the validity of section 503A. Congress otherwise left section 503A intact, including the requirement for drugs to be compounded based on the receipt of a valid patient-specific prescription.

The DQSA also added a new section 503B to the FD&C Act. In section 503B, Congress established a new, voluntary category of compounders known as outsourcing facilities. Like compounders that produce drugs under section 503A, outsourcing facilities compound drugs intended to meet the needs of specific patients for whom an approved or over-the-counter drug is not medically appropriate. However, outsourcing facilities can compound such drugs either pursuant to a patient-specific prescription or in response to an order from a health care provider, such as a hospital, without first obtaining patient-specific prescriptions.

If a compounder elects to become an outsourcing facility by registering with FDA, it must meet CGMP requirements, be inspected by FDA according to a risk-based schedule, report adverse events associated with its products to FDA, and meet certain other conditions in section 503B.

Drugs compounded by outsourcing facilities that meet the conditions in section 503B are exempt from three requirements of the FD&C Act:

- premarket approval requirements,
- the requirement for labeling with adequate directions for use, and
- drug supply chain security requirements.

The New Outsourcing Facility Sector

Outsourcing facilities range in size and may or may not obtain patient-specific prescriptions. Some outsourcing facilities operate on a large scale, distributing drug products without patient-specific prescriptions to health care facilities nationwide, while others are small and distribute drugs primarily within the state in which they are located pursuant to prescriptions for identified individual patients. Many outsourcing facilities are state-licensed pharmacies, but some are not, and many outsourcing facilities engage in patient-specific and non-patient specific compounding.

The CGMP requirements, enhanced oversight, and other conditions in section 503B are important because outsourcing facilities may distribute large quantities of compounded drugs to health care facilities nationwide without receiving patient-specific prescriptions.

As of November 27, 2016, 67 compounders are [registered](#) with FDA as outsourcing facilities. FDA encourages health care facilities that purchase compounded drugs to obtain them from outsourcing facilities because they are subject to increased quality standards and federal oversight.

Outsourcing facilities also differ with respect to the types of drugs produced. Some outsourcing facilities compound and distribute thousands of different drug products, while others compound and distribute just a few. The number of units (e.g., vials or syringes) of each drug product compounded can also vary tremendously, with some outsourcing facilities producing large batches of 100,000 units, and other outsourcing facilities producing small batches of less than 10 units. In addition, while all outsourcing facilities compound sterile drugs, many also compound non-sterile drugs, and most, but not all, outsourcing facilities compound drugs from bulk drug substances. The types of drug products compounded by outsourcing facilities include, for example, ophthalmics, anesthetics, antibiotics, hormones, steroids, dermatologic products, and vitamin injections.

FDA encourages entities, such as hospitals, that purchase compounded drugs, to obtain the drugs from outsourcing facilities. This is because there are greater assurances of quality when drugs are compounded by outsourcing facilities that meet the conditions of section 503B and CGMP requirements than there are for drugs compounded by entities that are not required to comply with CGMP requirements and are not routinely overseen by FDA.

However, drugs compounded by outsourcing facilities pose more significant risks than FDA-approved drugs from conventional manufacturers. In contrast to FDA-approved drugs, drugs compounded by outsourcing facilities are not subject to requirements relating to premarket review for safety and efficacy or manufacturing quality, labeling with adequate directions for use, and drug supply chain security.



FDA Oversight of Drug Compounders and Implementation of the Compounding Provisions of the FD&C Act

Following the fungal meningitis outbreak and enactment of the DQSA FDA acted quickly to increase its drug compounding oversight, develop policies regarding the compounding provisions of federal law, convene and obtain input from an advisory committee, and collaborate with state regulators and stakeholders on compounding regulation.

Regulatory Oversight

As of November 27, 2016, FDA has:

- **Conducted more than 350 inspections, including 85 inspections of outsourcing facilities.**

Nearly 120 of the 350 inspections have been for-cause, typically based on reports of serious adverse events or product quality issues, such as drug contamination. The remaining inspections were risk-based surveillance inspections or inspections to follow up on corrective actions implemented after regulatory actions or previous inspections. FDA issued a [Form FDA 483](#), which identifies inspectional observations from FDA investigators, at the conclusion of almost all of these inspections. Many compounders have recalled drug products or ceased operations to address observations made during FDA inspections that indicate that the drug products may have been contaminated or otherwise poor quality.

FDA does not interact with the vast majority of the thousands of compounders who seek to operate under section 503A of the FD&C Act because these compounders are not licensed by FDA and generally do not register their compounding facilities with FDA. Therefore, FDA is often not aware of potential problems with their compounded drug products or compounding practices unless it receives a complaint such as a report of adverse event or visible contamination. States are primarily responsible for the day-to-day oversight of these compounders.

- **Issued more than 130 [warning letters](#) advising compounders of significant violations of federal law.**

Most of these warning letters describe failure to meet certain conditions of sections 503A or 503B, as applicable, and insanitary conditions. FDA expects firms to undertake corrective actions after receiving a warning letter, and the agency then conducts follow-up inspections to evaluate the adequacy of their corrective actions. Compounders that do not come into compliance may be subject to enforcement action, such as seizure, injunction, or criminal prosecution.

- **Issued more than 30 letters referring inspectional findings to state regulatory agencies.**

These letters are issued when, based on FDA's inspection, a state-licensed pharmacy appears to obtain valid prescriptions for identified individual patients, has committed to taking any necessary corrective actions, and FDA believes that needed corrective actions can be appropriately overseen by the state.

- **Overseen about 100 recalls involving compounded drugs.**

In many cases, compounders recalled all unexpired drug products on the market that were intended or expected to be sterile due to insanitary conditions at their facilities that resulted in a lack of sterility assurance. Other recalls involved sub- or super-potent drug products.

- **Worked with the Department of Justice on a number of civil and criminal enforcement actions.**

Four compounders entered into consent decrees of permanent injunction, which are court orders that prevent them from engaging in some or all operations until they comply with the FD&C Act, FDA regulations, and the terms of the order. Officials from two compounding facilities pled guilty to misdemeanor criminal violations of the FD&C Act. The government has also unsealed criminal indictments in two other cases.

Policy Development and State and Stakeholder Collaboration

As of November 27, 2016, FDA has:

- **Issued 18 draft guidances, seven final guidances, two proposed rules, a final rule, and a draft memorandum of understanding.**

The policy documents address many of the most significant compounding provisions of the law and are an important part of FDA's efforts to communicate with stakeholders about its regulatory policies, and to protect patient health from the risks associated with compounded drugs. FDA has received thousands of comments on its draft guidances and other policy documents and has been carefully considering them in finalizing its policies.

- **Held four intergovernmental working meetings with states in addition to numerous one-on-one meetings and interactions.**

FDA discusses with state regulators its compounding oversight and its efforts to implement the law, and identifies opportunities to better protect the public health with improved federal-state collaboration at intergovernmental working meetings. In addition, FDA routinely meets with and responds to inquiries and other correspondence from officials from states and national organizations, including the National Association

of Boards of Pharmacy and Federation of State Medical Boards. Topics of discussion include emerging public health concerns pertaining to compounding and, as appropriate, particular compounders; ways to improve collaboration and oversight; and policy matters. FDA also has worked with state officials to enter into information sharing agreements that permit the agency to disclose certain non-public information under federal law to facilitate close collaboration.

- **Re-established the Pharmacy Compounding Advisory Committee (PCAC) and held six meetings.**

The PCAC provides FDA advice on scientific, technical, and medical issues concerning certain provisions of sections 503A and 503B. For example, section 503A requires that FDA consult the PCAC as it develops the list of bulk drug substances that can be used in compounding under section 503A.

- **Held four sets of listening sessions with more than 75 stakeholders including pharmacy, hospital, long-term care, and other medical organizations; consumer and patient advocacy groups; insurers; and outsourcing facilities.**

These listening sessions have provided FDA with valuable feedback on its proposed policies and issues of concern to different groups that the agency considers in making decisions about how to implement the law.



FDA's efforts since enactment of the DQSA have resulted in significant progress. Many of the compounders that FDA inspected over the past several years have addressed troubling practices that put the public health at risk by implementing corrective actions or ceasing operations. In many cases, the compounders took these steps as a result of FDA regulatory actions. In addition, FDA's policy development, aided by state and stakeholder input, have brought needed clarity to certain regulatory requirements for compounders.

Photos of insanitary conditions taken during FDA inspections of drug compounders. Insanitary conditions can cause drugs to become contaminated and lead to serious patient injury or death.



Medical supply waste and dust built up in the pre-filter of an ISO-5 hood where drugs were compounded.



Visible mold contamination on ceiling tiles removed from room where compounding occurred.



Exposed insulation in ceiling above doorway to a cleanroom.



Dead cockroach on the floor of a compounding room.

Continuing FDA's Compounding Oversight and Implementation to Protect the Public Health

FDA continues to be concerned about the risk to patients from drugs compounded by facilities that do not comply with the conditions in sections 503A or 503B, as relevant, or other applicable requirements of the FD&C Act. For example, during inspections, FDA investigators have identified many compounders that were not registered as outsourcing facilities, but were engaged in large-scale, non-patient specific compounding like a conventional manufacturer, without complying with premarket approval, labeling, and CGMP requirements for their drugs. While FDA has taken steps to encourage these compounders to voluntarily comply with the FD&C Act, such as issuing warning letters, FDA has found during follow-up inspections that many compounders continue to fail to comply with applicable requirements of the law.

Of particular concern is that FDA continues to observe insanitary conditions during many of its inspections. Examples of insanitary conditions FDA has observed during its inspections include those pictured here, as well as toaster ovens used for sterilization; operators processing sterile drug products with exposed skin, which sheds particles and bacteria; and use of soap, tap water, and non-sterile disinfectants to clean and sanitize sterile compounding areas; among many others. Compounding drugs under insanitary conditions creates a significant risk of contamination that could lead to widespread patient harm, especially when the compounder engages in large-scale, non-patient specific compounding and distribution. FDA may not be aware of which compounders are making such drugs, and some states may have insufficient resources to adequately oversee them. In such cases, patients in the other states into which the pharmacy ships are placed at significant risk. For example, during the 2012 fungal meningitis outbreak, the Centers for Disease Control and Prevention reported that patients in 20 states, but not in the pharmacy's home state, were injured.

FDA also continues to receive reports of serious adverse events and product quality defects, including contamination, related to sterile and non-sterile compounded drugs. Some examples include:

- In 2016, FDA alerted health care professionals of a voluntary recall of a [compounded morphine sulfate injectable drug product](#) after laboratory results showed the product was super-potent by 2,460 percent. FDA is aware of serious adverse events

in three infants associated with the use of the recalled morphine sulfate product. Injecting a patient with super-potent morphine could result in serious consequences including respiratory depression, coma, and death.

- In 2015, FDA alerted health care professionals and patients of a voluntary recall of [compounded multivitamin capsules](#) containing high amounts of Vitamin D₃ (cholecalciferol), distributed nationwide by a compounder. FDA received several reports of adverse events potentially associated with these compounded capsules. FDA warned that consuming this drug product may result in vitamin D toxicity, which may be life-threatening if left untreated.
- In 2013, a compounder recalled all purportedly sterile drugs within expiry and ceased sterile operations after 15 patients developed bacterial bloodstream infections, and two patients died, from an infusion of contaminated [compounded calcium gluconate](#). FDA identified insanitary conditions at the facility and confirmed bacterial contamination in the calcium gluconate.
- In 2013, 26 patients experienced adverse events, including skin abscesses, after receiving injections of [methylprednisolone acetate](#) that a compounder distributed to health care facilities in 17 states. The compounder recalled all purportedly sterile drug products within expiry and ceased sterile operations after FDA identified insanitary conditions at the facility and confirmed bacterial contamination in drug products.

These and many other events are indicative of the work that still needs to be done. FDA is actively working to bring compounders into compliance with the applicable requirements of federal law and thereby lower the risk that compounded drugs pose to patients.

FDA is also actively working to further improve collaboration with state officials. States are primarily responsible for day-to-day oversight over the vast majority of the thousands of pharmacists, pharmacies, and physicians in the United States who engage in compounding, most of whom do not register with FDA. Therefore, state officials may be the first to identify compounders that are operating like conventional manufacturers or that engage in poor drug production practices that could lead to patient harm. It is critical that FDA and the states continue to work together to identify and take appropriate action against compounders whose practices present the greatest risk to public health.

Without all of these efforts, it will be more likely that another outbreak like the devastating 2012 fungal meningitis outbreak will occur again.

Conclusion

As evidenced by the 2012 fungal meningitis outbreak and other serious adverse events associated with compounded drugs, which have included outbreaks of infections and deaths, robust oversight over human drug compounding is critical to protect public health. Since enactment of the DQSA, FDA has devoted significant resources to the oversight of compounding and implementation of the compounding provisions of the law.

FDA is committed to building on the progress it has made over the last several years by finalizing draft guidance documents and proposed rules based on stakeholder feedback, proposing policies in draft guidance documents and proposed rules for public comment, convening additional PCAC meetings, and continuing to collaborate with states and communicate with stakeholders. FDA also intends to continue to actively oversee drug compounders, and, when appropriate, take regulatory action.

Such efforts are necessary to protect patients from the risks associated with compounded drug products that are not produced in accordance with applicable requirements of federal law, while preserving access to lawfully-marketed compounded drugs for patients who have a medical need for them.



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