A pharmacist-driven Food and Drug Administration incident surveillance and response program for compounded drugs

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Purpose. To provide an overview of compounding under sections 503A and 503B of the Federal Food, Drug, and Cosmetic Act, and to describe the pharmacist's role within the US Food and Drug Administration's (FDA's) Compounding Incidents Program, whose efforts are aimed at protecting the public against poor-quality compounded drugs through surveillance, review and response to adverse events and complaints.

Summary. Compounded drugs may serve an important medical need for patients who cannot be treated with medications approved by FDA; however, compounded drugs are not approved by FDA and are not subject to premarket review for safety, efficacy, or manufacturing quality; thus, they may pose safety risks to patients. Prompt reporting of adverse events or complaints related to compounding is important in identifying these risks and implementing safeguards to protect the public. FDA's Compounding Incidents Program consists of a team of pharmacists dedicated to the surveillance and review of adverse events and complaints and follow-up actions related to safety risks associated with compounded drugs. Pharmacists are a vital component of FDA's Compounding Incidents Program, utilizing their clinical skill set and regulatory knowledge to review and act on safety issues that affect public health.

Conclusion. As FDA continues to expand the Compounding Incidents Program and its efforts to protect the public against poor-quality compounded drugs, we encourage the continued submission of adverse event reports by healthcare professionals and consumers to FDA's MedWatch reporting system in addition to adverse event reporting compliance by outsourcing facilities.

Keywords: United States Food and Drug Administration, drug compounding, adverse drug event, adverse drug reaction reporting systems

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The US Food and Drug Administration (FDA) generally regards compounding as the combining, admixing, mixing, diluting, pooling, reconstituting, or otherwise altering of a drug or bulk drug substance to create a drug product.[1] Compounded drugs can serve an important patient need and may be medically necessary. For example, if a patient has an allergy to an inactive ingredient in a commercial product, or if a particular dose, dosage form, or drug combination is not commercially available, a compounded drug would be necessary to meet that particular patient's needs. However, compounded drugs are not approved by FDA and therefore have not undergone premarket review by the agency for safety, efficacy, or manufacturing quality. As such, compounded drugs can pose health risks. For example, compounded drugs made using poor-quality compounding practices may be sub- or superpotent, contaminated, or otherwise adulterated. FDA has historically received many reports of cases of serious patient injury linked to poor-quality compounded drugs. The risks associated with compounded drugs were brought to the forefront in 2012 when contaminated intrathecal and intra-articular drugs compounded at the New England Compounding Center in Massachusetts led to more than 750 cases of fungal meningitis and more than 60 patient deaths in 20 states.[2]

In 2013, in response to the fungal meningitis outbreak, Congress passed the Drug Quality and Security Act (DQSA), which (as described further below) amended the Federal Food, Drug, and Cosmetic Act (FD&C Act). As a result of the DQSA, 2 provisions in the FD&C Act apply to human drug compounding, sections 503A and 503B.[3,4]

Section 503A, which had initially been added to the FD&C Act by the Food and Drug Administration Modernization Act of 1997, describes the conditions that must be met for

drug products compounded by a licensed pharmacist in a state-licensed pharmacy or federal facility, or by a licensed physician, to qualify for exemptions from 3 key provisions of the FD&C Act. These provisions pertain to approval of drugs under new drug applications (NDAs) or abbreviated new drug applications (ANDAs) (section 505 of the FD&C Act[5]), labeling of drugs with adequate directions for use (section 502(f)(1) of the FD&C Act[6]), and current good manufacturing practice (CGMP) requirements (section 501(a)(2)(B) of the FD&C Act[7]).

In 2013, the DQSA eliminated the provisions of section 503A concerning advertising of compounded drugs that had been found to be unconstitutional, thereby removing uncertainty about the validity of section 503A, and added section 503B to the FD&C Act in response to the 2012 fungal meningitis outbreak.

Section 503B describes the conditions that must be met for drug products compounded in an outsourcing facility under the supervision of a pharmacist to qualify for exemptions from sections 505, 502(f)(1), and the drug supply chain security requirements (section 582) of the FD&C Act.[5,6,8] Outsourcing facilities remain subject to CGMP requirements and must meet certain other conditions, such as reporting adverse events and providing FDA with certain information about the products they compound. A compounder engaged in sterile compounding operations may elect to register as an outsourcing facility, and FDA inspects these facilities according to a risk-based schedule. Approximately 73 entities are registered with FDA as outsourcing facilities.[9] Information regarding outsourcing facilities, including past product reports, is available on FDA's website.[10] The website also includes information about inspections, recalls, and other actions regarding compounding.[11]

Since enactment of the DQSA, FDA has devoted resources to implement many programs aimed at enforcing the provisions of the FD&C Act in an effort to protect the public from unsafe and poor-quality compounded drugs. FDA works with stakeholders, such

as state regulatory authorities, to ensure transparency and collaboration on important safety issues. Some examples of state regulatory authorities that FDA has communicated and collaborated with include state boards of pharmacy, departments of health, and nursing boards and chiropractic boards, to name a few.[12] Due to the safety issues and risks posed by poor-quality compounded drugs, the Compounding Incidents Program was conceived to track, review, take action, and address adverse events and complaints.

Compounding Incidents Program

The Compounding Incidents Program includes dedicated pharmacists whose mission is to protect the public against unsafe compounded drugs. This is accomplished through surveillance, research and follow-up, and action to address incidents as well as through communications to raise stakeholder and public awareness of safety issues related to compounding. An incident is either a report of an adverse event or a complaint associated with a compounded drug, including product quality issues. FDA defines an adverse event as any untoward medical occurrence associated with the use of a drug in humans, whether drug related or not.[13] A complaint is a report not related to an adverse event regarding topics such as potential copies of FDA-approved drugs and potential adulteration issues, such as insanitary conditions.

Surveillance. The role of the pharmacist in the Compounding Incidents Program is vital to the process of surveilling incidents related to compounded drugs. A report generated from FDA's Adverse Event Reporting System (FAERS) that identifies cases related to compounded drugs or compounding firms is reviewed daily. This report includes voluntary MedWatch reports from consumers, patients, and healthcare professionals, as well as mandatory reports from outsourcing facilities. Review of the reports can be complex

and time-consuming due to the large proportion of reports (>90%) that appear to be related to compounding but are “false positives” because the word “compounded” appears on the report in a different context or a reporter mistakenly selects “compounded” as the product type on a MedWatch form concerning an FDA-approved, commercially manufactured product. A pharmacist’s clinical expertise is important to correctly identify reports of safety and product quality issues associated with compounded drugs.

In addition to MedWatch reports, the pharmacist also reviews reports from other sources, such as FDA’s Division of Drug Information and state regulatory authorities. Once a case has been reviewed and determined to be compounding related, the case is then entered into a database. The database provides the ability to search for trends that may alert the Compounding Incidents Program to potential safety issues associated with compounded drugs.

Research and follow-up. Most of the reports received by the Compounding Incidents Program lack the information necessary to thoroughly assess the incident. Part of the investigative process involves the pharmacist contacting the reporter to gather additional information. The pharmacist also conducts research on the compounding pharmacy or 503B outsourcing facility that made the product, including FDA history regarding past incidents, inspections, and regulatory and enforcement actions. Drug information research and literature searches on the incident are performed to review what is known about the adverse effect and the drug, as needed. Physician assessment of adverse event reports, such as whether the adverse event is related to a product quality issue or clinical issue, are also incorporated into the pharmacist’s overall evaluation of the incident. In addition, relevant FDA guidance documents or past FDA actions on the topic are considered to ensure a consistent approach to regulations and response.

The pharmacist presents pertinent information collected during the incident investigation to the Incident Coordination Group. This group is a multidisciplinary collaboration among different offices within FDA that address compounding issues, including offices with expertise in manufacturing and pharmaceutical quality, drug information, and pharmacovigilance, among others. In addition to presenting the case findings, the pharmacist recommends the most appropriate action to address the particular incident.

Action. Multiple actions can be taken to ensure appropriate responses to incidents are achieved and to protect the public from unsafe compounded drugs. These actions may include (1) further investigation, (2) inspections, (3) recalls, (4) sample collection and testing, (5) issuance of notification letters of safety issues to state boards, and (6) public communications alerting healthcare professionals, compounders, and patients of adverse events, drug quality concerns, or other compounded drug–related issues that pose a public health risk, known as a Compounding Risk Alert (CRA). For some incidents, the case may require multiple actions to ensure safety risks are mitigated. The investigation process and the available portfolio of actions are continuously adapted and expanded in response to new incidents of different complexities and new topics.

Discussion of real-life examples provides a more in-depth look into the investigation process of the Compounding Incidents Program. The following examples highlight some of the risks associated with compounded drugs and how the Compounding Incidents Program worked to mitigate or eliminate them.

Example cases. The example cases summarized below highlight the importance of voluntary submission of adverse event reports by healthcare professionals. Further harm to the public may have resulted if these incidents had not been voluntarily reported to FDA.

In 2017, the Compounding Incidents Program received 2 MedWatch reports from healthcare professionals regarding intravenous (IV) turmeric (also known as curcumin) compounded by ImprimisRx, located in Irvine, CA. One report involved cardiac arrest, and later death, in a 30-year-old female patient. The second report involved a hypersensitivity reaction in a 71-year-old male patient. Both cases required the pharmacist in the Compounding Incidents Program to perform extensive research and follow-up to gather patient information, details surrounding the adverse events, provider information, compounder information, and safety and efficacy data on the IV administration of curcumin. The pharmacist worked with multiple FDA offices and state regulatory authorities to investigate these cases. FDA collected and analyzed samples of the IV bag containing curcumin solution administered to the female patient, as well as the vial of compounded curcumin emulsion used to prepare the IV bag. They found that both the solution and the emulsion contained only about 1% to 2% of the labeled concentration.

FDA also identified the presence of an impurity known as diethylene glycol (DEG), a central nervous system depressant and potent kidney and liver toxin commonly used in antifreeze and brake fluids, in an amount of 0.21% weight per weight. As a result of these investigations into the 2 incidents, an inspection of ImprimisRx was initiated and the curcumin emulsion products were recalled. In addition, FDA's first-ever CRA was issued to share its findings about these 2 cases involving compounded curcumin.[14] Since then, CRAs have become a useful method of public communication for alerting healthcare professionals of adverse events and outbreaks related to compounded drugs.

In another example, FDA received reports of overdoses of fentanyl and ketamine injectable products compounded by outsourcing facilities. The dosing errors were attributed to confusion about the labeled strength expression of the compounded injectable products.

Conventional manufacturers label their injectable products with the strength per total volume as the primary and prominent expression of strength on the label, consistent with FDA's April 2013 draft guidance and the labeling requirements set forth in the *United States Pharmacopeia–National Formulary* in general chapter 7, "Labeling."[15,16] Some compounders, however, label their injectable products differently. For example, FDA has received multiple complaints raising concerns that displaying the strength per milliliter instead of the strength per total volume in a larger, more prominent font might lead to confusion about the amount of drug in the container. To address this potential safety issue, FDA issued a CRA to raise awareness of differences in labeling practices between conventional manufacturers and compounders.[17] The manner in which the strength is displayed on the product label may lead to dosing errors when healthcare professionals, who are more familiar with conventional manufacturers' expressions of strength information, are administering compounded drugs.

Compounding metrics. Historically, the Compounding Incidents Program has received around 200 adverse event or complaint reports per fiscal year (Figure 1). However, in fiscal year 2020 we saw a significant increase in the number of reports received. Figure 2 shows an 81% year-over-year increase in the volume of reports in quarter 1 and a 123% increase in quarter 2. Outreach efforts targeting outsourcing facilities and the public and our collaborative work with the state boards of pharmacy have helped to increase the awareness and importance of reporting adverse events associated with compounded drugs.

In response to many of these incident reports and other program inspectional initiatives, from 2013 to 2020 the Compounding Program worked with FDA's Office of Regulatory Affairs to conduct over 780 inspections, issue over 245 warning letters advising compounders of significant violations of federal law, issue more than 160 letters referring

inspectional findings to state regulatory agencies, and oversee over 250 recalls involving compounded drugs; and worked with the Department of Justice on more than a dozen injunctions, amongst other civil and criminal enforcement actions. As FDA continues to be alerted to potential safety issues with compounded drugs, the Compounding Incidents Program expands on its processes and services to discover potential risks associated with compounded drugs and to implement safeguards to protect the public.

FDA's Compounding Program has grown since the DQSA was enacted in 2013. But as the data and examples presented here highlight, there is still much to do to achieve compliance in the compounding industry and protect the public against unsafe compounded drugs.

Importance of adverse event reporting

Compounded drugs are not FDA approved and are not subject to the extensive rigors of the regulatory approval process to ensure safety, efficacy, and quality before they reach patients. FDA has identified many cases of serious patient injury linked to poor-quality compounded drugs.

Outsourcing facilities are required to submit all reports of serious and unexpected adverse events associated with the use of their compounded prescription drug products to FDA. These reports must be submitted electronically through the Safety Reporting Portal or Electronic Submissions Gateway, in accordance with section 503B of the FD&C Act and FDA's guidance document titled "Adverse Event Reporting for Outsourcing Facilities Under Section 503B of the Federal Food, Drug, and Cosmetic Act."[4,18] Traditional pharmacies, such as state-licensed pharmacies and hospital pharmacies, operate in accordance with section 503A of the FD&C Act; however, generally, they do not submit reports of adverse events

associated with their compounded drugs to FDA. Therefore, FDA may not be aware of certain adverse events or quality issues, which is why voluntary reporting of adverse events by healthcare professionals and consumers through MedWatch is critical. Such reports enable FDA to identify safety signals and potential quality issues associated with compounded drugs that are not captured through the required reporting by outsourcing facilities.

Information related to compounded drugs received through voluntary MedWatch report submissions is individually reviewed by the pharmacist in the Compounding Incidents Program to determine if FDA action is warranted. Often, the investigation of adverse event reports reveals substandard processes or conditions at an outsourcing facility or a traditional pharmacy that may call into question the quality of the compounded drugs produced in the facility. In order to ensure the Compounding Incidents Program receives the reports for review and investigation, products must be appropriately designated as compounded in the "product type" section of the report. Figure 3 provides helpful tips on how to report an adverse event associated with a compounded drug on the MedWatch form. FDA is grateful to healthcare professionals and consumers who have submitted adverse event reports for compounded drugs and encourages their continued submission via the MedWatch portal.[19] We understand there are limitations that may make reporting difficult (eg, limited information about the event, time constraints on medical staff who are busy caring for patients). In order to submit a MedWatch report, reporters should provide a description of the adverse event or problem, the name of the suspect product, and their name, at minimum. If an adverse event or safety issue associated with a compounded product is suspected, it can be reported to FDA by telephone at 1-800-FDA-1088 or submitted online at https://www.accessdata.fda.gov/scripts/medwatch/.

MedWatch reports that FDA receives are housed in the FAERS database, which is designed to support the agency's safety surveillance program. The FAERS Public Dashboard is an interactive, Web-based tool specifically designed for public viewing and querying of FAERS data.[20] It is intended to expand access to the public and increase the transparency of the adverse event reports submitted to FDA.

Conclusion

Compounded drugs can meet important medical needs for patients who cannot be treated with FDA-approved drugs. However, compounded drugs may pose unique risks to patients because they do not undergo premarket review by FDA for safety, efficacy, or quality. Prompt, detailed, and accurate reporting of adverse events or complaints related to compounded drugs is imperative to enable FDA to protect the public against unsafe compounded drugs. Pharmacists are in a unique position to identify issues with compounded drugs and can serve an important role in relaying those issues to FDA. Through surveillance, follow-up, and action to address incidents, the Compounding Incidents Program aims to mitigate risk and raise public awareness of safety issues related to compounded drugs. Pharmacists, utilizing their clinical skill set and regulatory knowledge to review and act on safety issues affecting public health, are a vital component of the Compounding Incidents Program. Pharmacists can stay up-to-date on FDA actions related to compounding by joining FDA's compounding listserver.[1]

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Disclosures

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References

1. US Food and Drug Administration. Human drug compounding. Accessed December 15, 2020. https://www.fda.gov/drugs/guidance-compliance-regulatory-information/human-drug-compounding
2. US Food and Drug Administration. Multistate outbreak of fungal meningitis and other infections. Accessed April 28, 2020. https://www.fda.gov/drugs/drug-safety-and-availability/multistate-outbreak-fungal-meningitis-and-other-infections
3. Federal Food, Drug, and Cosmetic Act, 21 USC §353a (2013).
4. Federal Food, Drug, and Cosmetic Act, 21 USC §353b (2013).
5. Federal Food, Drug, and Cosmetic Act, 21 USC §355 (2010).
6. Federal Food, Drug, and Cosmetic Act, 21 USC §352(f)(1) (2018).
7. Federal Food, Drug, and Cosmetic Act, 21 USC §351(a)(2)(B) (2017).
8. Federal Food, Drug, and Cosmetic Act, 21 USC §360eee-1 (2018).
9. US Food and Drug Administration. Registered outsourcing facilities. Accessed August 24, 2020. https://www.fda.gov/drugs/human-drug-compounding/registered-outsourcing-facilities
10. US Food and Drug Administration. Information for outsourcing facilities. Accessed August 24, 2020. https://www.fda.gov/drugs/human-drug-compounding/information-outsourcing-facilities
11. US Food and Drug Administration. Compounding: inspections, recalls, and other actions. Accessed February 14, 2020. https://www.fda.gov/drugs/human-drug-compounding/compounding-inspections-recalls-and-other-actions

12. US Food and Drug Administration. Compounding information for states. Accessed December 3, 2020. https://www.fda.gov/drugs/human-drug-compounding/compounding-information-states
13. New Drugs, Records and Reports. CFR §310.305 (2014).
14. US Food and Drug Administration. FDA investigates two serious adverse events associated with ImprimisRx's compounded curcumin emulsion product for injection Published August 4, 2017. Accessed February 14, 2020. www.fda.gov/drugs/human-drug-compounding/fda-investigates-two-serious-adverse-events-associated-imprimisrxs-compounded-curcumin-emulsion
15. US Food and Drug Administration. Guidance for industry: safety considerations for container labels and carton labeling design to minimize medication errors. Published April 2013. Accessed February 14, 2020. www.fda.gov/media/85879/download
16. United States Pharmacopeia. 38(1) In-process revision: LABELING [NEW] (USP36-NF31). Accessed February 14, 2020. www.uspnf.com/sites/default/files/usp_pdf/EN/USPNF/revisions/m4908-general-chapter_7.pdf
17. US Food and Drug Administration. Differences in strength expression on product labels of compounders and conventional manufacturers may lead to dosing errors. Published September 2018. Accessed February 14, 2020. www.fda.gov/drugs/human-drug-compounding/differences-strength-expression-product-labels-compounders-and-conventional-manufacturers-may-lead
18. US Food and Drug Administration. Guidance for industry: adverse event reporting for outsourcing facilities under section 503B of the Federal Food, Drug, and Cosmetic Act.

Published October 2015. Accessed February 14, 2020. www.fda.gov/media/90997/download

19. US Food and Drug Administration. MedWatch online voluntary reporting form. Accessed February 14, 2020. www.accessdata.fda.gov/scripts/medwatch/
20. US Food and Drug Administration. FDA Adverse Event Reporting System (FAERS) Public Dashboard. Accessed February 14, 2020. www.fda.gov/drugs/questions-and-answers-fdas-adverse-event-reporting-system-faers/fda-adverse-event-reporting-system-faers-public-dashboard

Figure 1. Total number of incidents (adverse events and complaints) reported to FDA's Compounding Incidents Program by fiscal year (FY).

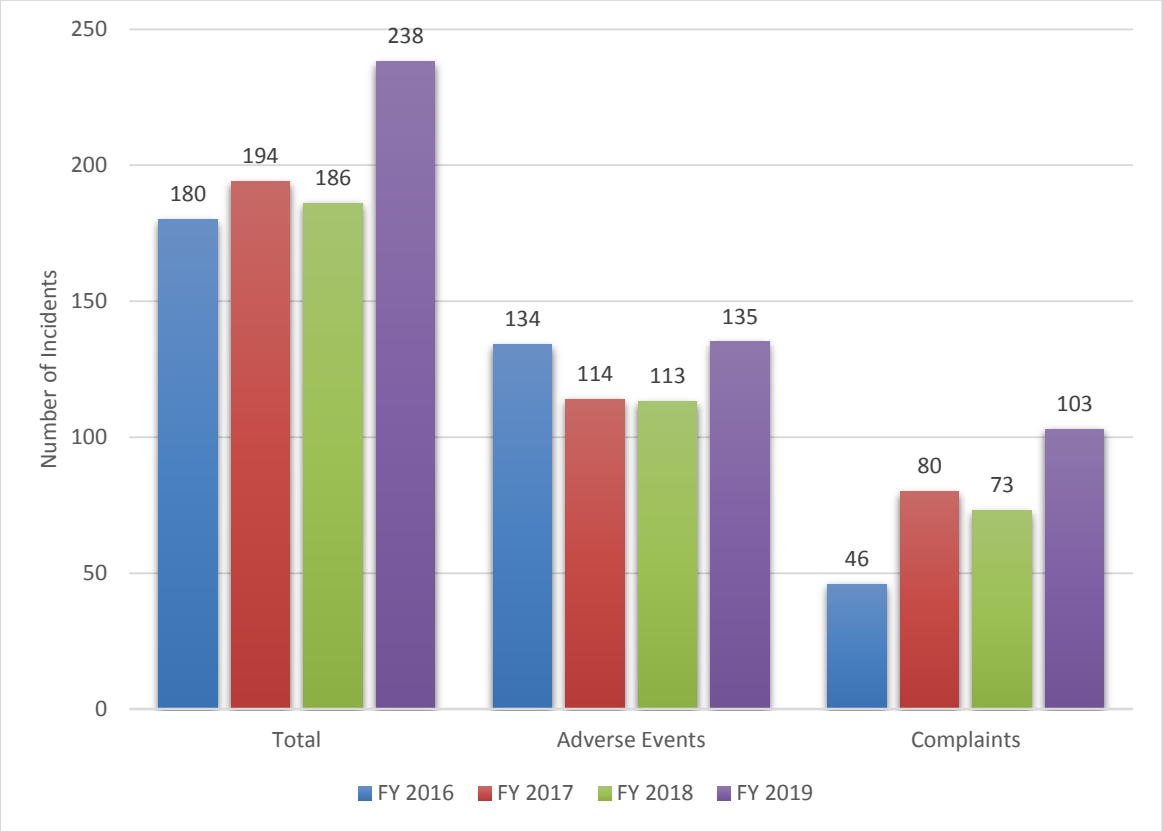
Figure 2. Comparison of incidents reported to FDA's Compounding Incidents Program in quarters 1 and 2 of fiscal year (FY) 2019 and FY 2020, depicting a large increase in reports in FY 2020.

Figure 3. Helpful tips on reporting an adverse event associated with a compounded drug on the FDA MedWatch form.

Key Points

- Compounded drugs are not approved by the US Food and Drug Administration (FDA) nor subject to premarket review for safety, efficacy, or manufacturing quality and may thus pose safety risks to patients.
- Prompt reporting of adverse events or complaints related to compounding from consumers and healthcare professionals is important in identifying these risks and implementing safeguards to protect the public.
- FDA's Compounding Incidents Program is dedicated to surveillance and follow-up actions related to safety risks associated with compounded drugs.

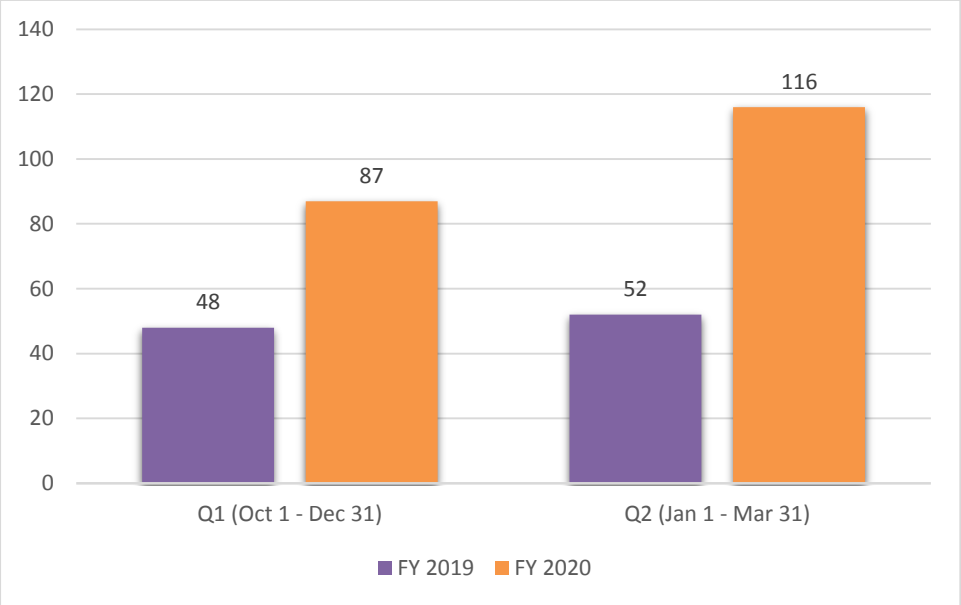
Figure 1



Total Incidents by Fiscal Year

	Total	Adverse Events	Complaints
FY 2016	180	134	46
FY 2017	194	114	80
FY 2018	186	113	73
FY 2019	238	135	103

Figure 2



Quarter Comparison

	Q1 (Oct 1 - Dec 31)	Q2 (Jan 1 - Mar 31)
FY 2019	48	52
FY 2020	87	116

Figure 3

How to indicate a product is compounded on the FDA MedWatch form

There are two electronic forms available for reporting adverse events on the FDA MedWatch website[19]:

- Select the appropriate form for health professional (FDA Form 3500) or consumer/patient (FDA Form 3500B).
  - Provide as much detail as possible about the adverse event when completing the form.
  - For the section **product type,** there are 4 options which are slightly different depending on the form chosen (see table below).
    - On the form, click the blue circle to get additional information related to each product type to help you decide which choice is most appropriate.

Healthcare Professional Form	Consumer/Patient Form
Product Type: ❑ OTC (Over-The-Counter) ❑ Compounded ❑ Generic ❑ Biosimilar	**Product Type:** ❑ OTC (Over-The-Counter) ❑ Compounded by a Pharmacy or an Outsourcing Facility ❑ Generic ❑ Biosimilar

Is the product that I am reporting considered compounded?

NO	YES
• The product is FDA approved and prepared according to the product labeling.	• The provider stated that the medication required customization for patient-specific needs. • The pharmacy or physician mixed several ingredients to create a product tailored to the needs of the patient. • The product label states "This is a compounded drug" and that it was produced by an outsourcing facility. • When I looked up the product manufacturer online, it was listed as a 503B outsourcing facility.