



# **FDA Enforcement Update**

## **Inter-governmental Working Meeting on Drug Compounding September 20, 2016**

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# FDA Regulatory Actions

## Examples of factors to consider:

- The nature of the violation
- Risk to public health
  - Lack of sterility assurance
  - Actual contamination
- Prior violations
- The overall adequacy of the firm's corrective action
- Whether documentation of the corrective action was provided

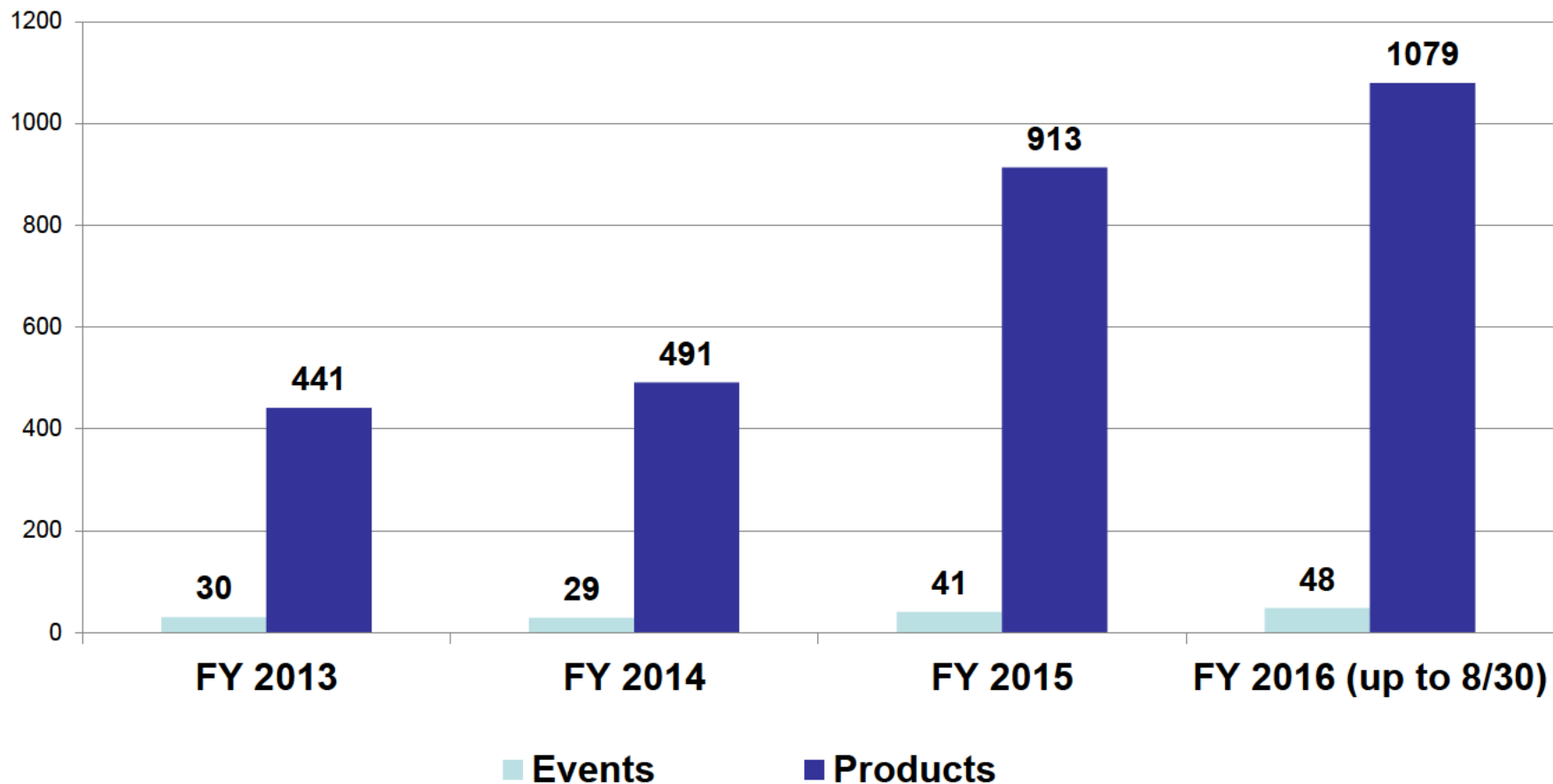
# Voluntary Actions

- **Recalls**

- Since October 2012 there have been over 100 recall events involving compounded drugs, many due to conditions and practices resulting in a lack of drug sterility assurance
  - Some recalls overseen by FDA, others overseen by the state
  - FY 2013 – 30 recall events
  - FY 2014 – 29 recall events
  - FY 2015 – 41 recall events
  - FY 2016 – 48 recall events (as of August 30, 2016)
- Since October 2012 FDA has issued 4 letters requesting firms to recall compounded drugs after they refused recommendations to recall compounded drugs



# Compounding Recalls



The total number of products is misrepresented in some events. A large number of products were characterized as 1 product described as "all products".

# Voluntary Recalls: Examples

- 11/25/2015 - Voluntary recall of compounded multivitamin capsules containing high amounts of Vitamin D3 (Cholecalciferol), distributed nationwide by Glades Drugs in Pahokee, Florida. FDA received reports of several adverse events potentially associated with these compounded capsules made by Glades Drugs.
- 1/16/2016 - Voluntary recall by Abbott's Compounding Pharmacy of all unexpired lots of sterile compounded products due to concerns of lack of sterility assurance.
- 3/30/2016 - Voluntary recall of all unexpired compounded drug products produced and distributed by Reliable Drug Pharmacy in San Francisco, due to concerns over mislabeled compounded drug products. FDA received two human adverse event reports from patients taking drug products labeled as biotin that were compounded by Reliable Drug.
- 4/19/2016 - Voluntary recall by Pharmakon Pharmaceuticals, Inc. of all lots of sterile products aseptically compounded and packaged by Pharmakon that remain within expiry due to FDA concern over a lack of sterility assurance and other quality issues. Pharmakon had recently recalled a morphine sulfate drug product that was 2460% superpotent.

# Warning Letters

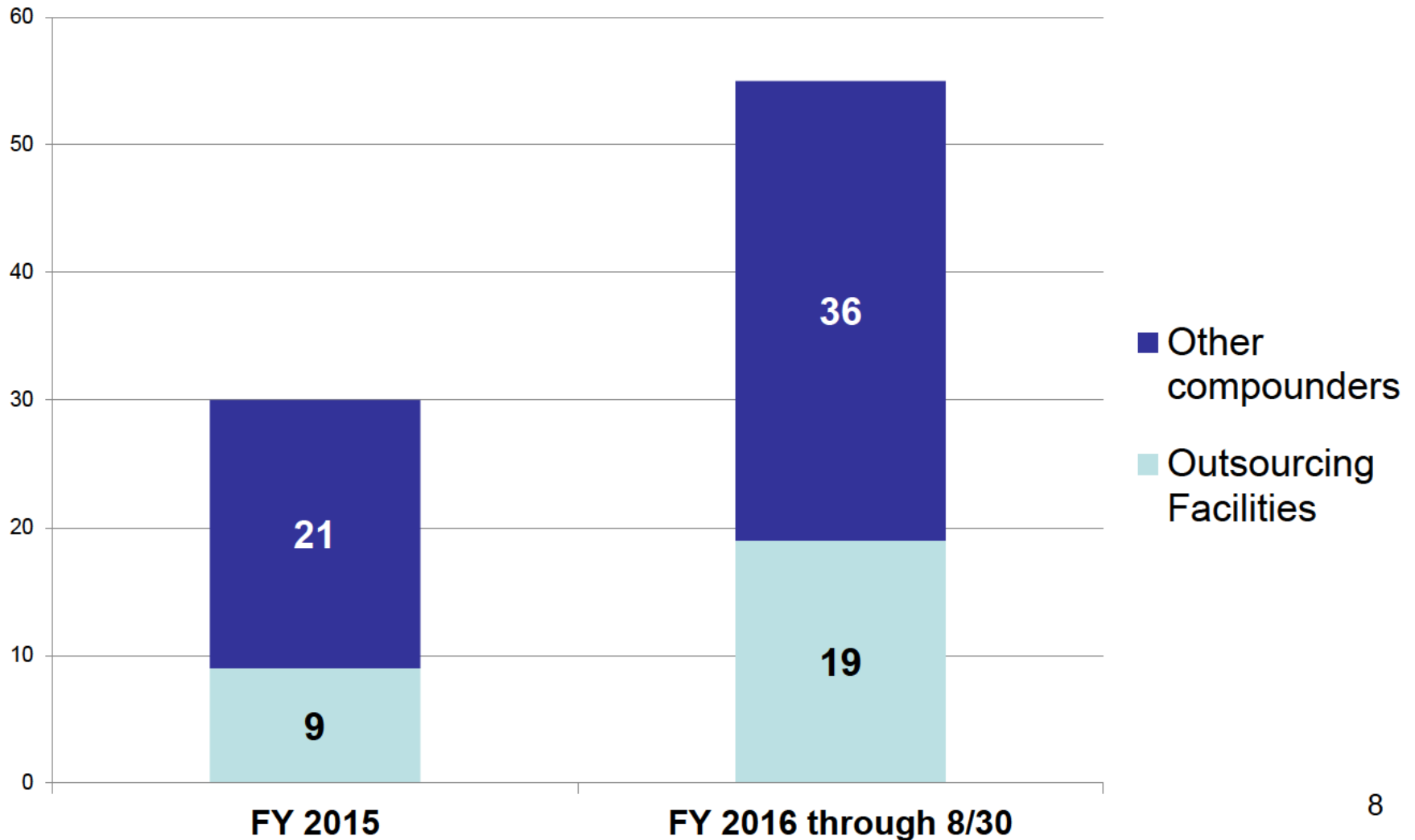
- Advisory actions – provide notice
- Communicate the Agency's position
- Issued to achieve voluntary and prompt corrective action
- FDA may take enforcement action without issuing a warning letter when, for example, there is a history of repeat violations.

# Warning Letters

- FDA has issued over 100 warning letters since October 2012
- Many of the warning letters describe violations associated with insanitary conditions



# Warning Letters





# Warning Letters

In addition to insanitary conditions violations, if a firm is not registered as an outsourcing facility under section 503B of the FDCA and its drug products do not meet all of the conditions of section 503A, a warning letter may cite violations of requirements for new drug approval, labeling with adequate directions for use, and current good manufacturing practice

# Warning Letters

- In addition to insanitary conditions violations, warning letters to facilities registered as outsourcing facilities under section 503B may also include:
  - Violations of current good manufacturing practice (CGMP) requirements
  - Failure to meet the conditions of section 503B, such as
    - Failure to include appropriate labeling
    - Failure to submit required product reports

# Warning Letters

- Outsourcing facilities received about 40 of the 100+ warning letters issued since October 2012
- Several of the outsourcing facilities that received warning letters subsequently deregistered with FDA
  - Of note - about half of the compounders FDA has inspected whose drug products have not met the conditions of section 503A have subsequently registered with FDA as outsourcing facilities
- Unapproved new drug and misbranding violations may be included in warning letters to outsourcing facilities that fail to meet the conditions of section 503B

# Warning Letters: Examples

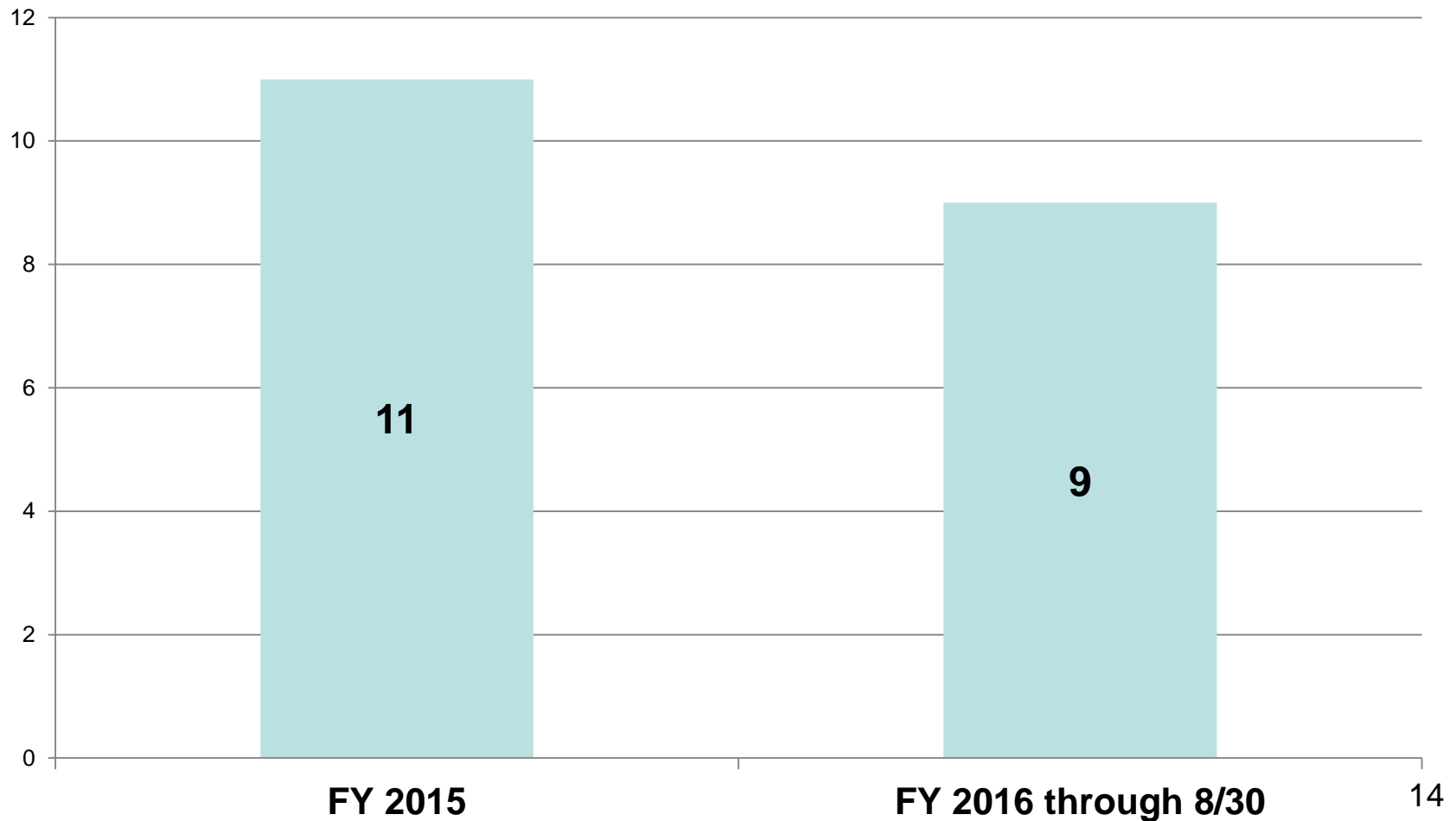
- Some examples of deviations from adequate sterile practices and conditions cited in recent warning letters include:
  - ISO 5 area contained peeling paint and dark yellow residues on the walls
  - Failure to monitor the pressure differential between ISO 7 cleanroom and ISO 8 anteroom
  - Failure to use sterile wipes or sterile disinfectants as part of the cleaning and disinfection program for the ISO 7 areas and the ISO 5 hood.
  - Exposed facial skin and facial hair
  - Failure to use an effective sporicidal agent
  - Failure to perform environmental monitoring for viable air in the ISO 5 zone
  - Processing sterile drug products in laminar flow hood that was not turned on
  - Ceiling tiles of ISO 7 cleanrooms were not fully sealed
  - Failure to perform adequate investigations of sterility failures
  - Batches found to contain particulates

# State Referral Letters

- State Referral Letters:
  - Sent to State Board of Pharmacy in the state in which the FDA-inspected compounding pharmacy is located when a
    - Pharmacy apparently compounds drugs in accordance with the provisions of section 503A (e.g., obtains prescriptions for identified individual patients); and
    - Pharmacy has promised to correct deviations, and Pharmacy's corrective actions can be appropriately overseen by the state
    - FDA has issued approximately 30 state referral letters since October 2012



# State Referral Letters



# Injunctions

- To prevent further production and/or distribution of adulterated, misbranded, and/or unapproved new drug products and to correct the root cause of the violations
- If a firm has a history of violations, and has promised to make corrections in the past, but has not made the corrections, an injunction may be more effective than other actions in stopping or preventing the violation.

# Injunction Process

- FDA drafts referral letter, complaint, and proposed consent decree and submits to the Department of Justice (DOJ)
- DOJ determines whether to pursue the case
- May issue “sign or sue” letter
- Attempt to negotiate consent decree
- File complaint in court



# Compounding Injunction Cases in FY 2016

## Paul Franck (FL)

- In April 2016, a federal judge entered an order of permanent injunction against Paul W. Franck of Ocala, Florida. According to the complaint, Franck manufactured and distributed drug products that were adulterated and misbranded in violation of the FDCA.
- Franck owned and operated numerous compounding pharmacies in Florida over the past 20 years, including Franck's Lab Inc., doing business as Franck's Compounding Lab, and Franck's Lab Inc., doing business as Trinity Care Solutions.
- In 2014, Trinity Care Solutions recalled all sterile drugs and ceased compounding operations after the FDA's inspection revealed violations such as the presence of dead spiders, beetles, ants, wasps and cockroaches in the ceiling panel directly above the area where employees prepare for sterile processing; lack of sufficient physical barriers to prevent the introduction of contamination from nearby construction into the clean room; and failure to adequately clean and sanitize sterile compounding areas.
- In 2012, contaminated ophthalmic drugs compounded by Franck's Compounding Lab were linked to at least 47 cases of eye infections, including at least 39 cases of temporary or permanent vision loss.

# Compounding Injunction Cases in FY 2016

## Downing Labs (TX)

- On January 8, 2016, a federal judge entered a consent decree of permanent injunction between the United States and Downing Labs LLC, of Dallas, Texas, and the company's co-owners
- According to the complaint filed with the consent decree, Downing Labs (formerly known as NuVision Pharmacy) manufactured and distributed purportedly sterile drug products that were adulterated because the drugs were made under insanitary conditions and in violation of current good manufacturing practice requirements under the FDCA.
- In October 2015, Downing Labs voluntarily conducted a nationwide recall of its purportedly sterile drug products due to a lack of sterility assurance and ceased sterile operations.

# Compounding Criminal Actions in FY 2016

## Meds IV (AL)

- On June 21, 2016, the Department of Justice announced that two Alabama pharmacists were sentenced to 12 and 10 months in prison for their roles in the distribution of adulterated drugs compounded at the now-defunct compounding pharmacy, Advanced Specialty Pharmacy dba Meds IV. They pleaded guilty in March 2016 to two misdemeanor violations of the FDCA.
- As charged in the information, Amino acid used in compounding the TPN by Meds IV was adulterated in the following ways: it consisted in whole or in part of a filthy, putrid, or decomposed substance, namely *Serratia marcescens* (*S. marcescens*) and it was prepared, packed, or held under insanitary conditions.
- The adulterated TPNs were associated with nineteen cases of infection, including nine deaths, in 2011.