U.S. FOOD & DRUG ADMINISTRATION

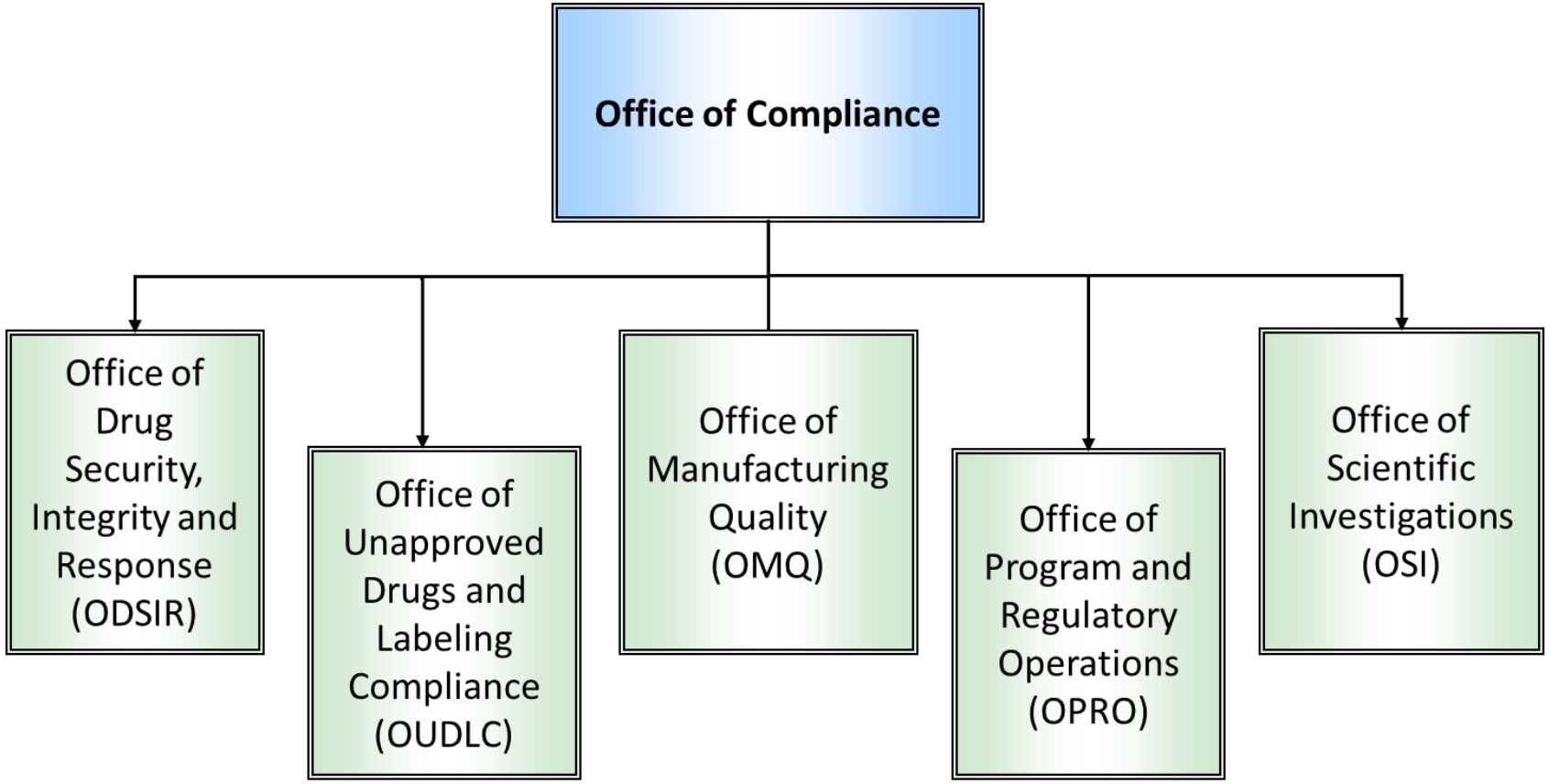
New Approach to Drug Inspections

Donald D. Ashley
Director – CDER Office of Compliance

2018 FDLI Annual Meeting

May 4, 2018

Office of Compliance Structure



Mission: The Office of Compliance shield's patients from poor quality, unsafe, and ineffective drugs through proactive compliance strategies and risk-based enforcement actions.

Agenda

- Concept of Operations and Facility Classification 90-Day Letters
- Developments in Drug Inspections: Over-the-Counter manufacturers
- New Inspection Protocol Project
- FDARA 806
- Compounding Risk Alerts

Concept of Operations ("ConOps")

- The Program Alignment initiative created a program-based management structure that aligns staff by FDA-regulated product.
- CDER and ORA developed a ConOps that outlines how CDER Compliance, Office of Pharmaceutical Quality and ORA will work within this environment, and applies to the following types of human drug facility inspections:
  - Pre- and post-approval inspections
  - For-cause inspections
  - Surveillance inspections
- CDER and ORA began to operationalize the ConOps in the fall of 2017

ConOps Highlights

What is different?

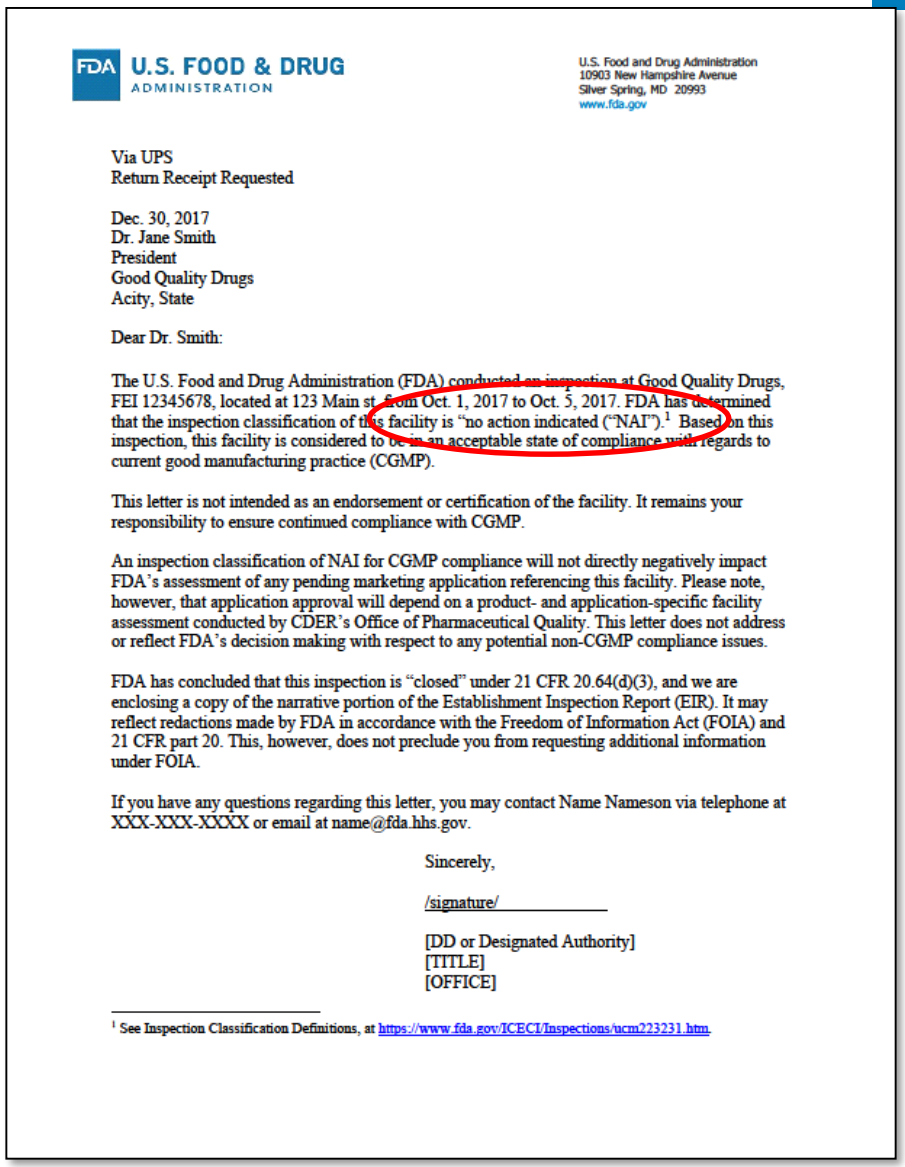
- Improved communication with stakeholders
- Defined timelines,
  - 90-Day decisional letters
  - 6-month goal for enforcement actions
- Parity between domestic and international inspections
- See the ConOps Q&A at: https://www.fda.gov/drugs/developmentapprovalprocess/manufacturing/ucm576309.htm

The 90-Day Letter

- Goal
  - Increase engagement with industry by communicating the final inspection classification to the facility within 90 days of the end of the inspection
- Scope
  - Applies to any CDER-led surveillance inspection
  - Includes “NAI” (No Action Indicated), “VAI” (Voluntary Action Indicated), and “OAI” (Official Action Indicated) letters
- GDUFA and ConOps
  - The 90-Day Letter was created to meet GDUFA II commitment and to achieve ConOps communication goals, by Oct 1, 2018.

The 90-Day NAI Letter

"FDA has determined that the inspection classification of this facility is "no action indicated ("NAI"). Based on this inspection, this facility is considered to be in an acceptable state of compliance with regards to current good manufacturing practice (CGMP)."



FDA U.S. FOOD & DRUG ADMINISTRATION

U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
www.fda.gov

Via UPS
Return Receipt Requested

Dec. 30, 2017
Dr. Jane Smith
President
Good Quality Drugs
Acity, State

Dear Dr. Smith:

The U.S. Food and Drug Administration (FDA) conducted an inspection at Good Quality Drugs, FEI 12345678, located at 123 Main st. from Oct. 1, 2017 to Oct. 5, 2017. FDA has determined that the inspection classification of this facility is "no action indicated ("NAI").[1] Based on this inspection, this facility is considered to be in an acceptable state of compliance with regards to current good manufacturing practice (CGMP).

This letter is not intended as an endorsement or certification of the facility. It remains your responsibility to ensure continued compliance with CGMP.

An inspection classification of NAI for CGMP compliance will not directly negatively impact FDA's assessment of any pending marketing application referencing this facility. Please note, however, that application approval will depend on a product- and application-specific facility assessment conducted by CDER's Office of Pharmaceutical Quality. This letter does not address or reflect FDA's decision making with respect to any potential non-CGMP compliance issues.

FDA has concluded that this inspection is "closed" under 21 CFR 20.64(d)(3), and we are enclosing a copy of the narrative portion of the Establishment Inspection Report (EIR). It may reflect redactions made by FDA in accordance with the Freedom of Information Act (FOIA) and 21 CFR part 20. This, however, does not preclude you from requesting additional information under FOIA.

If you have any questions regarding this letter, you may contact Name Nameson via telephone at XXX-XXX-XXXX or email at name@fda.hhs.gov.

Sincerely,

/signature/

[DD or Designated Authority]
[TITLE]
[OFFICE]

[1] See Inspection Classification Definitions, at https://www.fda.gov/ICECI/Inspections/ucm223231.htm

The 90-Day VAI Letter

Dear Mr. Jones:

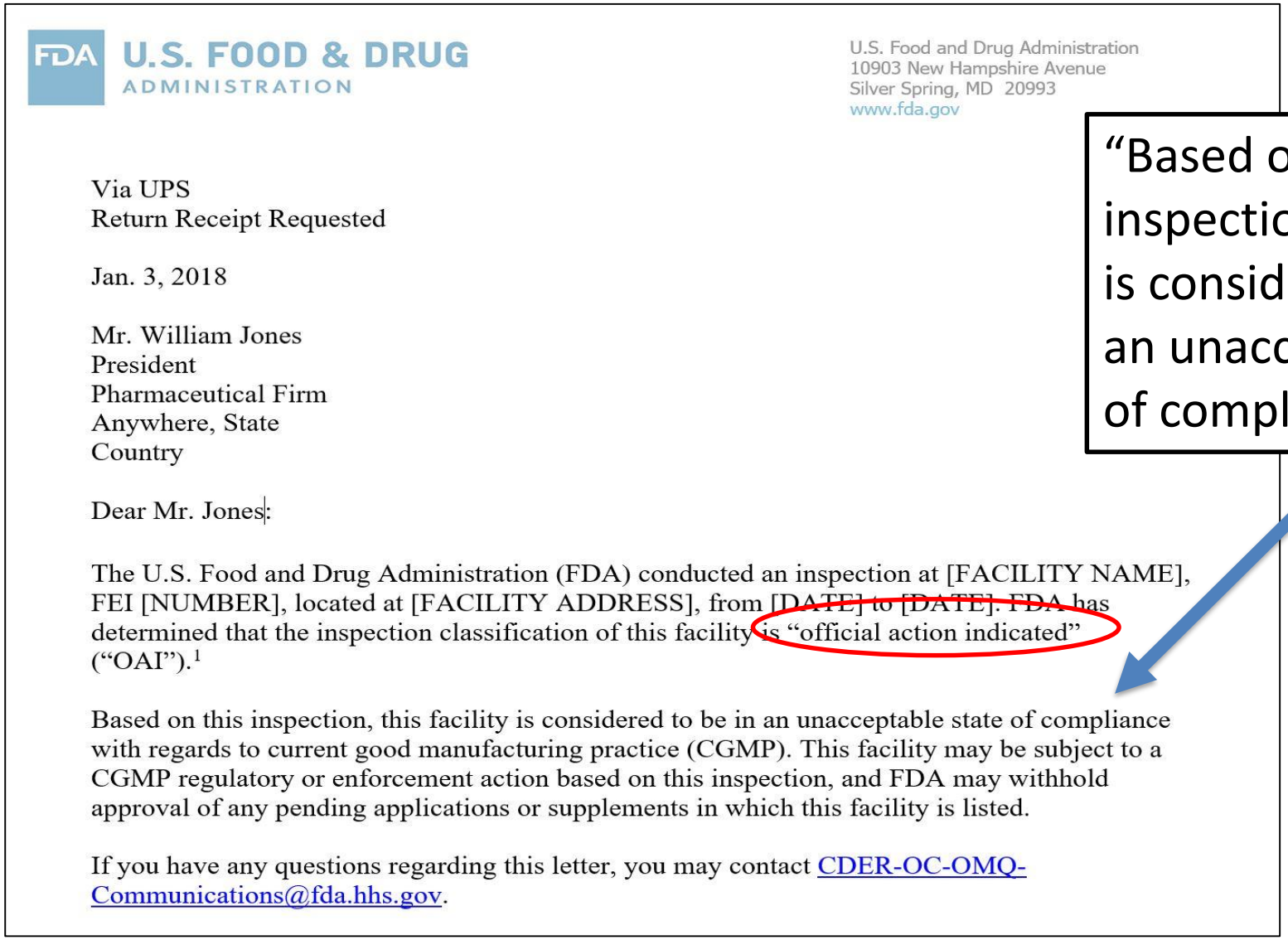
The U.S. Food and Drug Administration (FDA) conducted an inspection at [FACILITY NAME], FEI [NUMBER], located at [FACILITY ADDRESS], from [DATE] to [DATE]. FDA has determined that the inspection classification of this facility is "voluntary action indicated" ("VAI").[1] Based on this inspection, this facility is considered to be in a minimally acceptable state of compliance with regards to current good manufacturing practice (CGMP).

A VAI inspection classification indicates that, although investigators found and documented objectionable conditions during the inspection, FDA will not take or recommend regulatory or enforcement action because the objectionable conditions do not meet the threshold for action at this time. Despite this facility inspection classification, FDA recommends that you address any observations noted on the Form FDA 483 issued at the conclusion of the inspection or otherwise conveyed to you following the inspection. If not corrected, the same or similar conditions could lead to a future inspection being classified as "official action indicated" ("OAI").

This letter is not intended as an endorsement or certification of the facility. It remains your responsibility to ensure continued compliance with CGMP.

"…Based on this inspection, this facility is considered to be in a minimally acceptable state of compliance…"

The 90-Day OAI Letter



U.S. FOOD & DRUG ADMINISTRATION

U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
www.fda.gov

Via UPS
Return Receipt Requested

Jan. 3, 2018

Mr. William Jones
President
Pharmaceutical Firm
Anywhere, State
Country

Dear Mr. Jones:

The U.S. Food and Drug Administration (FDA) conducted an inspection at [FACILITY NAME], FEI [NUMBER], located at [FACILITY ADDRESS], from [DATE] to [DATE]. FDA has determined that the inspection classification of this facility is "official action indicated" ("OAI").[1]

Based on this inspection, this facility is considered to be in an unacceptable state of compliance with regards to current good manufacturing practice (CGMP). This facility may be subject to a CGMP regulatory or enforcement action based on this inspection, and FDA may withhold approval of any pending applications or supplements in which this facility is listed.

If you have any questions regarding this letter, you may contact CDER-OC-OMQ-Communications@fda.hhs.gov.

"Based on this inspection, this facility is considered to be in an unacceptable state of compliance…"

ConOps:
6 Month Enforcement Actions

- Goal
  - If an inspection is classified as final OAI, OMQ, solely or in collaboration with ORA, takes an appropriate action within 3 months of the decisional letter (6 months post-inspection)
- Scope
  - Applies to all follow-up actions, including regulatory meetings, warning letters, and import alerts
- Concept of Operations white paper:
  - *"[ConOps] will enable FDA to better handle the growing complexity of the pharmaceutical landscape and to meet new challenges by… improving the timelines for regulatory, advisory, and enforcement actions to protect public health and promote drug quality, safety, and effectiveness."*

ConOps: Office of Compliance Progress Toward 6 Month Enforcement Actions

From CY 2015 to present, there has been an overall average
51% improvement

2015	2016	2017	2018 (Jan-Mar)
Inspection Report Received by CDER to WL Issued	Inspection Report Received by CDER to WL Issued	Inspection Report Received by CDER to WL Issued	Inspection Report Received by CDER to WL Issued
10.8 months on average	**8.6 months on average**	**5.7 months on average**	**5.3 months on average**

Developments in FDA Drug Inspections: Over-the-Counter Drug Manufacturers

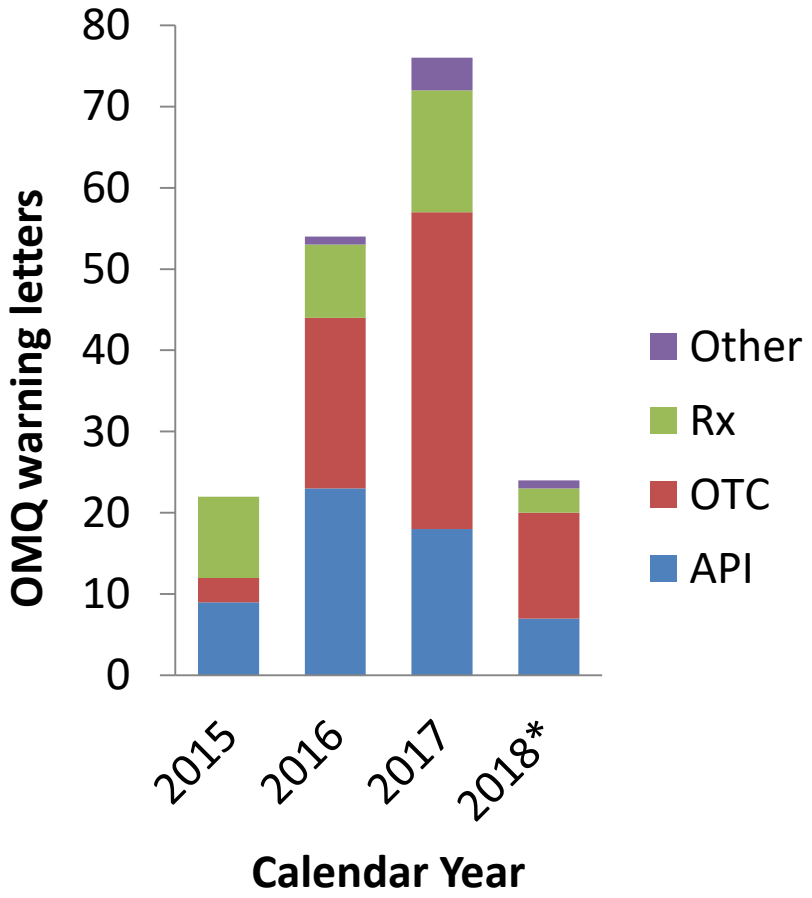
- FDA committed, in response to GAO, to inspect all of the previously never inspected foreign drug manufacturers over 3 years- from FY17 to FY19.
- This includes almost 1000 of the 3000 total foreign establishments.
- Many of these establishments are considered to manufacture “low-risk” OTC products, such as sunscreen and toothpaste
- FDA inspected, or removed from inventory, over 75% of these firms as of Dec. 2017
- FDA expects to have inspected, or removed, all of these firms by the end of FY18.

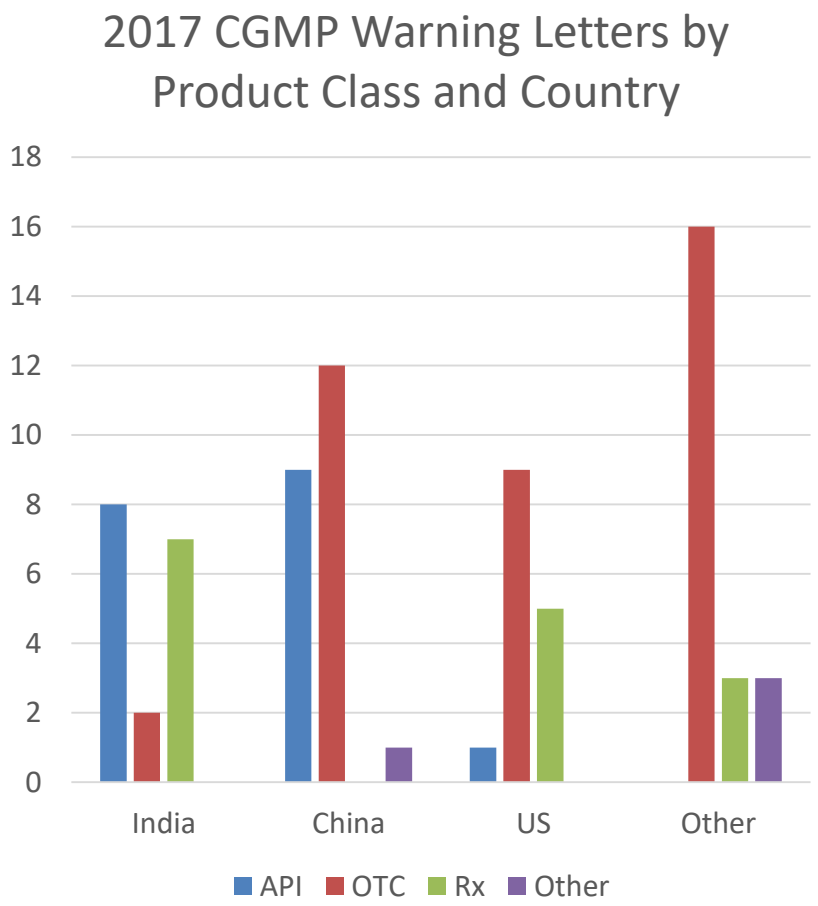
Inspectional Outcomes: Over-the-Counter Drug Manufacturers

- In 2017, 39 OTC manufacturers were issued Warning Letters and 36 OTC manufacturers were added to Import Alerts
- 12 OTC manufacturers have already been issued Warning Letters in 2018*
- Some of these firms had been previously inspected, but for many it was a first inspection
- Common observations include rudimentary CGMP and OTC ophthalmic drug products with particulate issues

*as of March 31, 2018

Inspectional Outcomes: CGMP Warning Letters





*To Mar. 31, 2018

The New Inspection Protocol Project (NIPP)

NIPP is a collaborative effort between the FDA's Office of Regulatory Affairs and Center for Drug Evaluation and Research. NIPP was launched to support the advancement of pharmaceutical quality by developing a new, more efficient inspection and reporting paradigm to better assess and record the state of quality in manufacturing facilities.

Areas of protocol and guidance development under NIPP:

- Surveillance inspections
- Pre-approval inspections
- Evidence development

NIPP - Status of Work

- The NIPP Surveillance, Pre-Approval, and Evidence Development working groups currently have pilots underway.

- These pilots are designed to assess the protocols and guidance:
  - Usability - the time and level of effort the draft protocols / guidance require of inspection personnel
  - Usefulness - the quality of information collected, developed, and reported during inspections to be used by surveillance, pre-approval, and compliance personnel post-inspection.

- The Evidence Development pilot is focused on guidance applicable to all CGMP inspections.

NIPP - Evidence Development

- This working group's efforts are intended to increase the efficiency of compliance review by making it easier to prioritize based on risk. This is incredibly important work because the Agency's CGMP compliance workload continually increases.

- How will this be accomplished?
  - Evidence Development guidance and work aids will highlight the development of information useful in assessing the potential for product quality and consumer impact.
  - These will help investigators understand of aggravating or mitigating circumstances that affect the risk associated with specific CGMP violations.

FDARA Overview

- FDA Reauthorization Act of 2017 (FDARA) reauthorized GDUFA II (in addition to other UFAs)
  - included several generics-related legislative "riders"
- FDARA went into effect on August 18, 2017, prior to start of GDUFA II on October 1, 2017
- Section 806 of FDARA adds a new requirement for FDA to generate and implement a protocol for expedited review of responses to inspectional observations, where the inspectional observations are the only barrier to approval of certain drug applications.

FDARA Sec. 806. Inspections

SEC. 806. INSPECTIONS.

Within 6 months of the date of enactment of this Act, the Secretary of Health and Human Services shall develop and implement a protocol for **expediting review of timely responses to reports of observations from an inspection** under section 704 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 374). Such protocol shall—

(1) apply to responses to such reports pertaining to applications submitted under section 505 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355)—

(A) for which the approval is dependent upon remediation of conditions identified in the report;

(B) for which concerns related to observations from an inspection under such section 704 are the only barrier to approval; and

(C) where the drug that is the subject of the application is a drug—

(i) for which there are not more than 3 other approved applications under section 505(j) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(j)) that reference the same listed drug and for which there are less than 6 abbreviated new drug applications tentatively approved; or

(ii) that is included on the list under section 506E of such Act (21 U.S.C. 356e);

(2) **address expedited re-inspection of facilities, as appropriate; and**

(3) **establish a 6-month timeline for completion of review of such responses to such reports.**

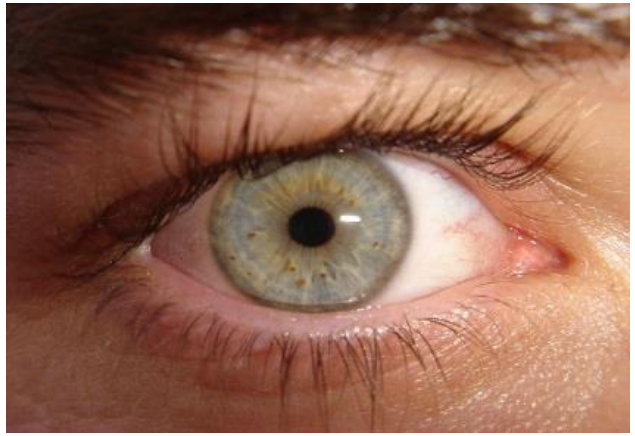
Compounding Risk Alerts: Rapid Communication of Inspectional Findings

- FDA began in 2017 to post "compounding risk alerts" to inform healthcare practitioners of adverse event reports associated with compounded drugs. https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm570188.htm
- FDA inspections or other actions may be are initiated when FDA receives adverse event reports from healthcare practitioners, patients, and others.
- FDA provides information in compounding risk alerts to health care professionals to further the goal of protecting patients from unsafe, ineffective, and poor quality compounded drugs.

Compounding Risk Alerts

2017: eye injections of a compounded drug linked to vision problems in 43 patients

- At least 43 patients received eye injections of a drug containing triamcinolone (steroid) and moxifloxacin (anti-infective) compounded by a Texas pharmacy.
- Patients developed vision impairment (blurred or decreased vision), loss of color perception, glare, halos, pain, and loss of balance among other symptoms.
- FDA alert: https://www.fda.gov/Drugs/DrugSafety/ucm569114.htm



Compounding Risk Alerts

2017: compounded curcumin product linked to one illness and one death

- Two patients given infusions of curcumin (a component of turmeric) compounded with polyethylene glycol (PEG) 40 castor oil experienced hypersensitivity reactions. One patient subsequently died.
- Risks illustrated by this case include the
  - Lack of a label warning about hypersensitivity reactions associated with PEG 40 castor oil
  - Use of a non-pharmaceutical grade ingredient containing impurities such as diethylene glycol
  - IV administration of curcumin when its safety profile by this route of administration and its effectiveness in treating eczema and thrombocytopenia have not been established

- FDA Alert: https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm570192.htm

THANK YOU