U.S. FOOD & DRUG ADMINISTRATION

Compliance Central with FDA CDER Compliance Director

Donald D. Ashley, J.D.

Enforcement, Litigation and Compliance Conference
December 12, 2018

Strategic Areas

1. Promote compliance
2. Risk-based regulatory and enforcement actions
3. Operational excellence

Drug Quality and Security Act

H. R. 3204

One Hundred Thirteenth Congress
of the
United States of America

AT THE FIRST SESSION

Begun and held at the City of Washington on Thursday, the third day of January, two thousand and thirteen

An Act

To amend the Federal Food, Drug, and Cosmetic Act with respect to human drug compounding and drug supply chain security, and for other purposes.

Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled,

SECTION 1. SHORT TITLE.

This Act may be cited as the "Drug Quality and Security Act".

SEC. 2. REFERENCES IN ACT; TABLE OF CONTENTS.

(a) REFERENCES IN ACT.—Except as otherwise specified, amendments made by this Act to a section or other provision of law are amendments to such section or other provision of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 301 et seq.).

(b) TABLE OF CONTENTS.—The table of contents of this Act is as follows:

TITLE I—DRUG COMPOUNDING

SEC. 101. SHORT TITLE.

This Act may be cited as the "Compounding Quality Act".

SEC. 102. VOLUNTARY OUTSOURCING FACILITIES.

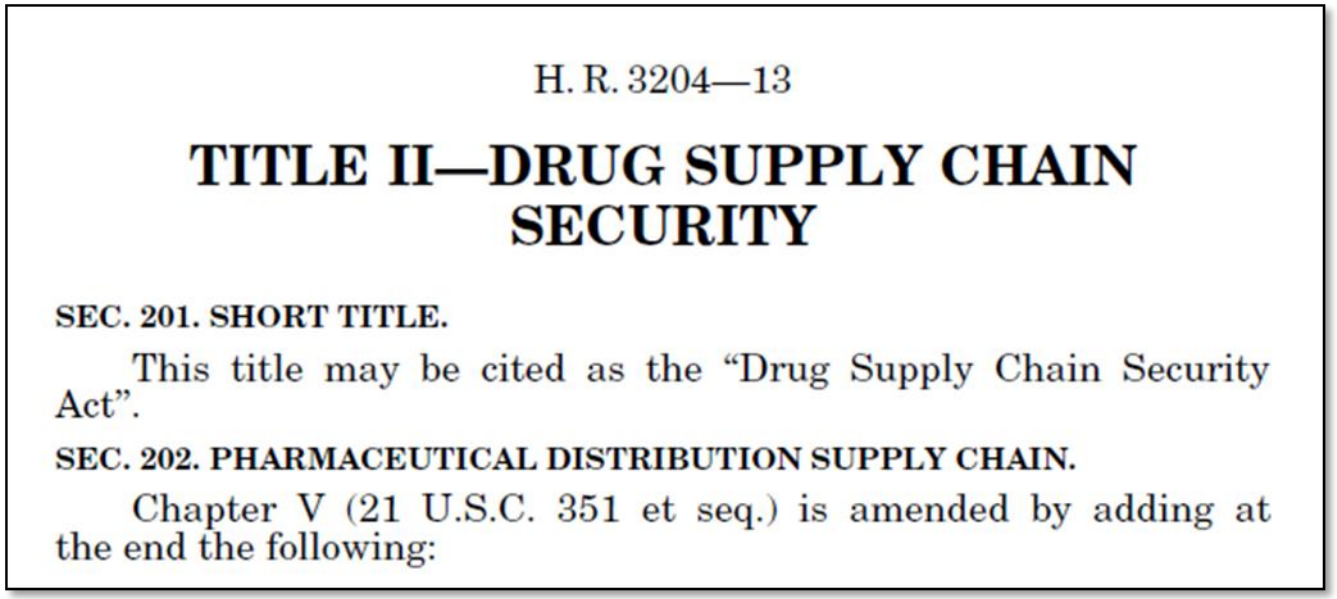
(a) IN GENERAL.—Subchapter A of chapter V (21 U.S.C. 351 et seq.) is amended—

Federal judge enters consent decree against Delta Pharma

Mississippi compounder prohibited from manufacturing and distributing violative drug products

Federal judge enters consent decree against Cantrell Drug Company

Compounder prohibited from manufacturing and distributing sterile drug products in violation of law



H. R. 3204—13

TITLE II—DRUG SUPPLY CHAIN SECURITY

SEC. 201. SHORT TITLE.

This title may be cited as the "Drug Supply Chain Security Act".

SEC. 202. PHARMACEUTICAL DISTRIBUTION SUPPLY CHAIN.

Chapter V (21 U.S.C. 351 et seq.) is amended by adding at the end the following:

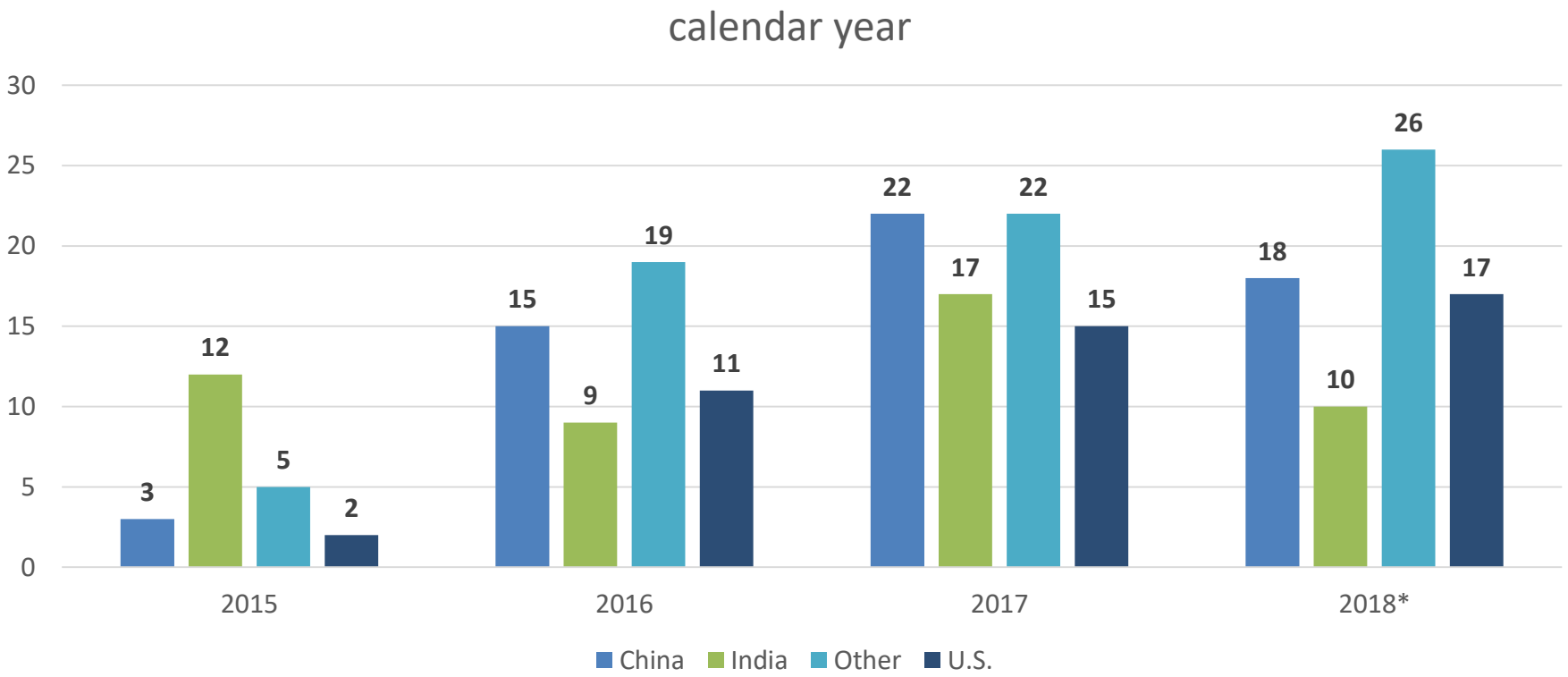
Product Identifier Requirements Compliance Policy

November 27, 2018

Administrative Detention Order

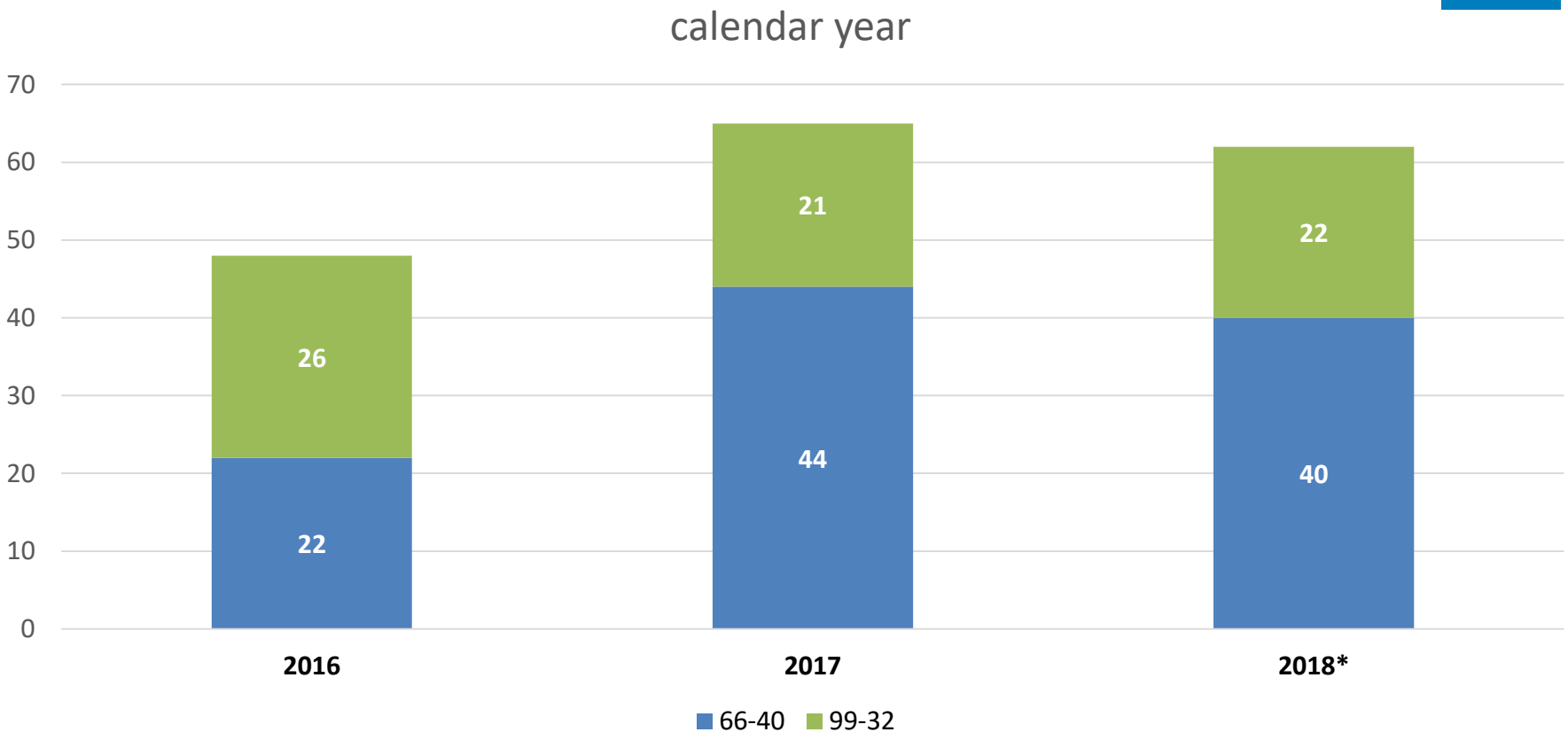
FDA seizes food and medical products held under insanitary conditions at an Arkansas grocery warehouse

CGMP Warning Letters



Excludes warning letters related to compounding
*data as of November 1, 2018

Import Alerts



*As of November 1, 2018.

Angiotensin II Receptor Blockers (ARB)

SHANGHAI/NEW YORK, Sept 28 (Reuters) - The U.S. Food and Drug Administration said on Friday it will no longer allow imports of drug ingredients or medicines made with ingredients produced at China's Zhejiang Huahai Pharmaceuticals Chuannan factory, after a recall of one of its drugs that contained a probable carcinogen.

2018 FDA Online Opioid Summit

"[W]e achieved our goal…to bring together the internet ecosystem and other stakeholders, including government, to begin the dialogue of how we can make a meaningful impact in decreasing the availability of opioids online."[12]

-FDA Commissioner Scott Gottlieb, M.D.

Opioid Warning Letters

An ongoing effort…

October 9, 2018
4 networks
including
approximately
300 websites

August 16, 2018
4 networks
including
approximately
20 websites

May 29, 2018
9 networks
including
approximately
50 websites

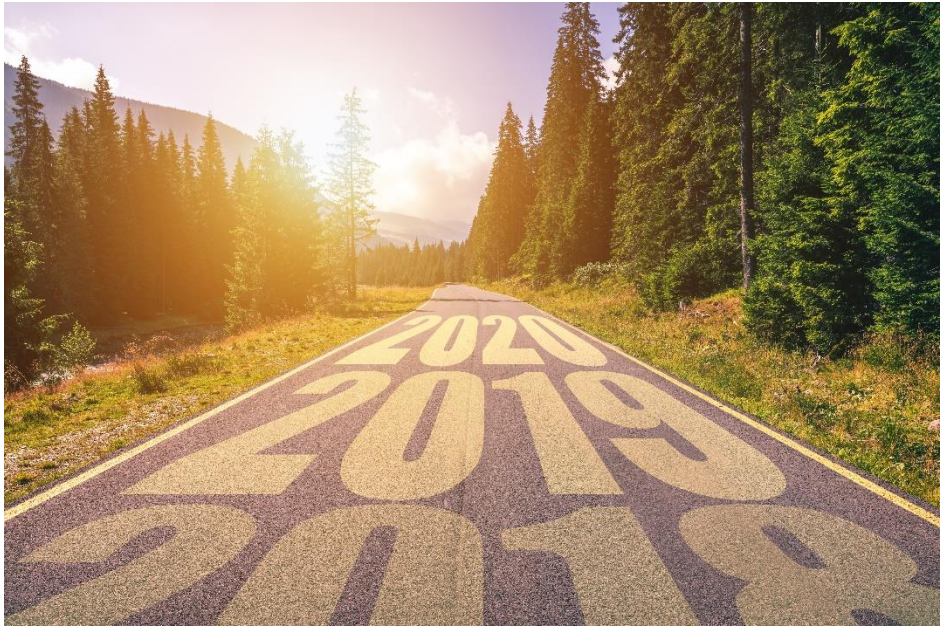
September 19, 2017
6 networks
including
approximately
100 websites

Health Fraud

FDA, FTC warn companies for selling illegal, unapproved opioid cessation products using deceptive claims

FDA warns companies selling illegal, unapproved kratom products marketed for opioid cessation, pain treatment and other medical uses

Looking ahead…



Opioids

Compounding

DSCSA

CGMPs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FDLI's Enforcement, Litigation and Compliance Conference

Compliance Central with FDA Compliance Center Compliance Directors

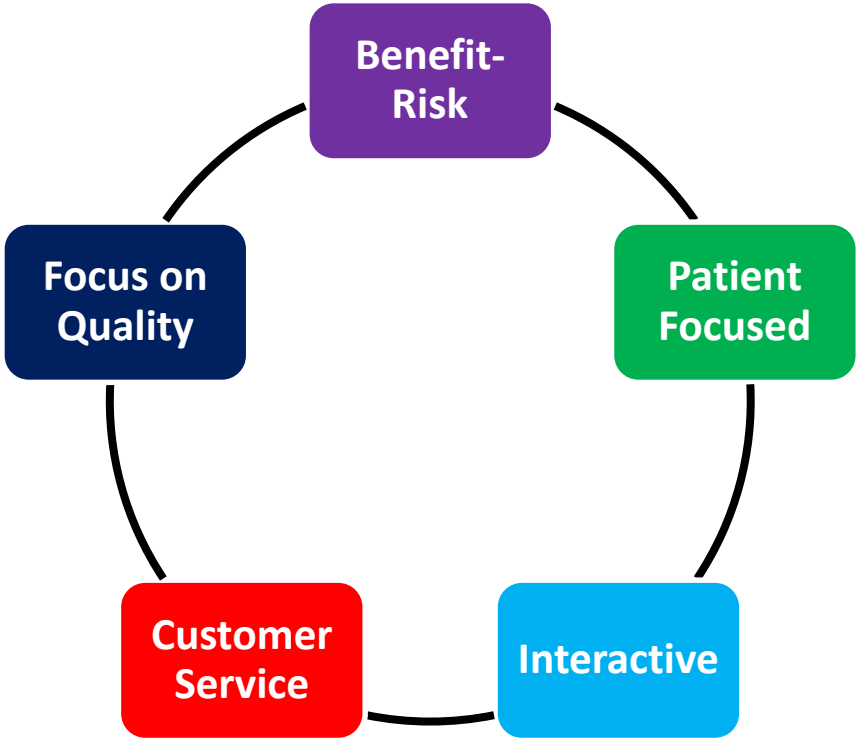
William Maisel, MD, MPH
Center for Devices and Radiological Health
U.S. Food and Drug Administration

Patients are at the Heart of What We Do

CDRH Vision

Patients in the U.S. have access to high-quality, safe, and effective medical devices of public health importance first in the world. Devices are legally marketed in the U.S. and remain safe, effective and high-quality.

Philosophies For Success



Application of Least Burdensome

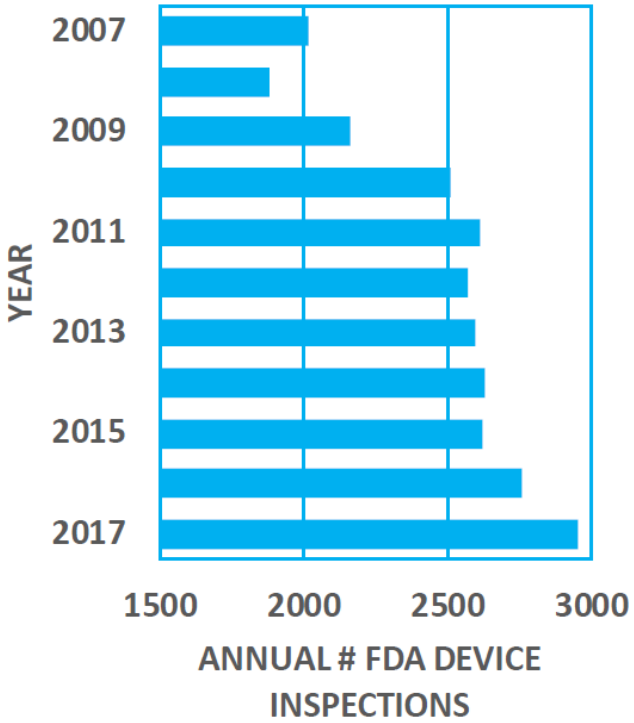
- 21st Century Cures updated the LB provisions and requires training of FDA staff
- CDRH believes LB applies to all activities related to medical device regulation
- Draft Guidance issued December 15, 2017

The minimum amount of information necessary to adequately address a regulatory question or issue through the most efficient manner at the right time.

FDA Reauthorization Act of 2017 (FDARA)

- Risk-based device establishment inspections (Section 701);
- Improvements to inspection process (Section 702);
- Reauthorization of inspection program (Section 703)
- Certificates to foreign governments for devices (Section 704)
- Facilitating international harmonization (Section 705)

Annual Number of Device Inspections



46% INCREASE

IN THE ANNUAL NUMBER OF DEVICE INSPECTIONS SINCE 2007.

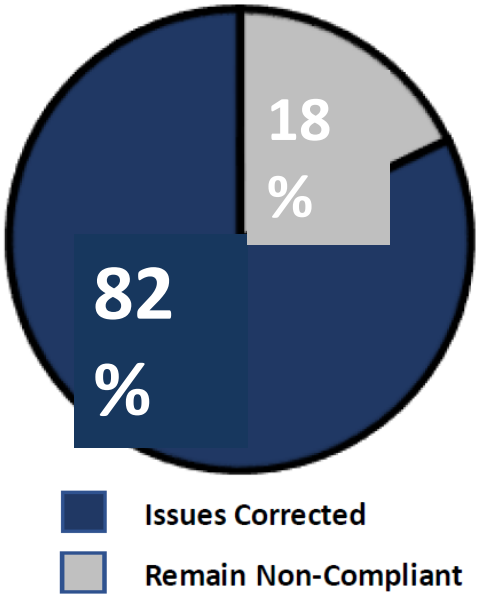
243% INCREASE

IN THE ANNUAL NUMBER OF FOREIGN DEVICE INSPECTIONS SINCE 2007.

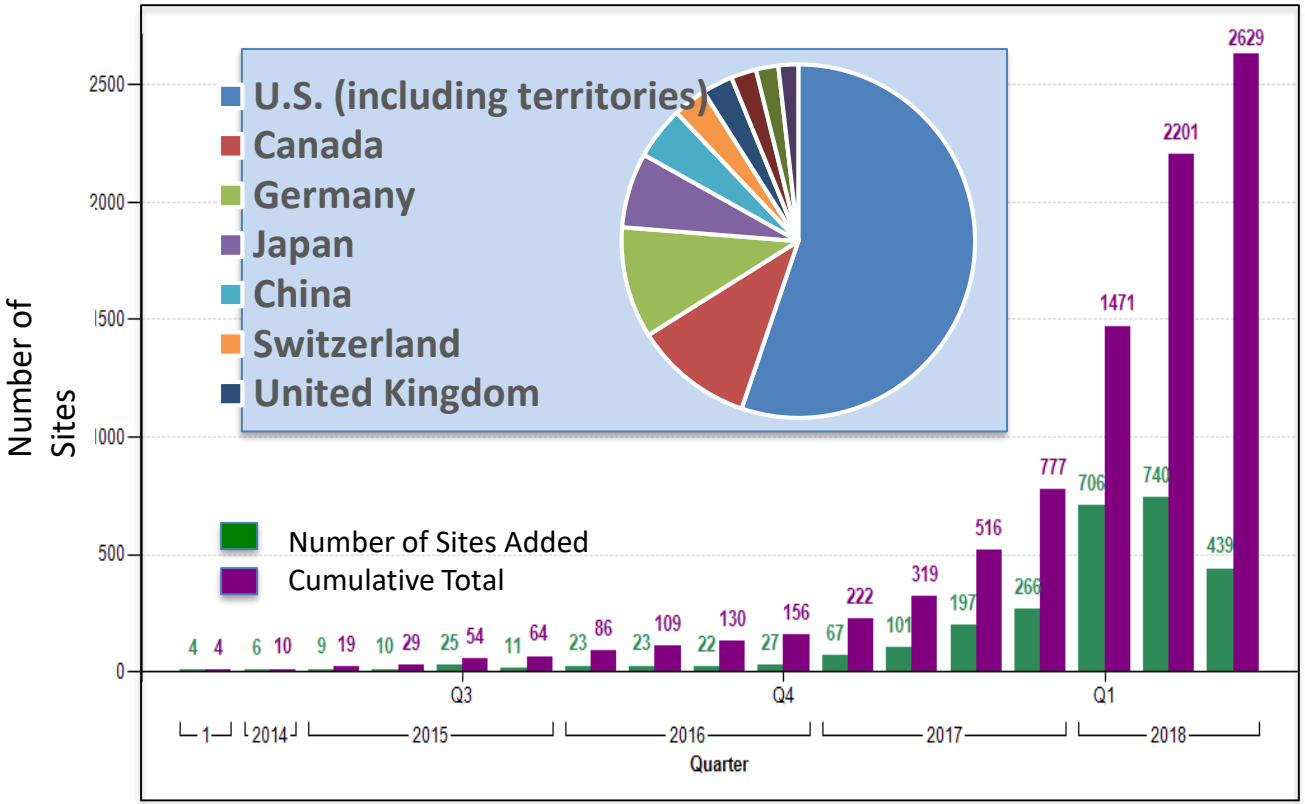
Most Firms Correct Device Violations On Follow-Up Inspection

82% of FIRMS

CORRECTED OBSERVED VIOLATIONS on FOLLOW-UP INSPECTION 2008-2017



MDSAP Participating Manufacturer Sites



What's the Vision for MDSAP in 2018 and Beyond?

- Deployment of information system to facilitate information sharing;
- Broader use of MDSAP audit reports by participating Regulatory Authorities;
- Inclusion of additional Regulatory Authorities
- Use of MDSAP audits by other regulators requiring compliance to ISO 13485;
- Increased harmonization among regulators.

FDA Quality System Regulation and 13485

- FDA announced its intention to harmonize and modernize the Quality System regulation for medical devices.
- The revisions will supplant the existing requirements with the specifications of ISO 13485:2016.
- The revisions will help harmonize domestic and international requirements.
- This approach is consistent with and complements MDSAP.
- FDA hopes to issue NPRM in 2019.

See Spring 2018 Unified Agenda of Regulatory and Deregulatory Actions at https://www.reginfo.gov/public/do/eAgendaViewRule?pubId=201804&RIN=0910-AH99

Novel Approaches to Promoting Product Quality

Case for Quality 2011

MDIC Collaborative Forum 2014

Voluntary Quality Maturity Appraisal Pilot 2018

- Third-party certified by Capability Maturity Model Integration Institute (CMMI) conducts appraisal
- Collaboration and feedback on quality objectives
- Removal from the surveillance work plan
- Reduction in manufacturing submission requirements and faster approval for implementation
- Waive some pre-approval inspections

- ✓ 18 participating firms
- ✓ 32 appraisals
- ✓ 86% report appraisal had a positive impact on product quality

Achieving Our Vision

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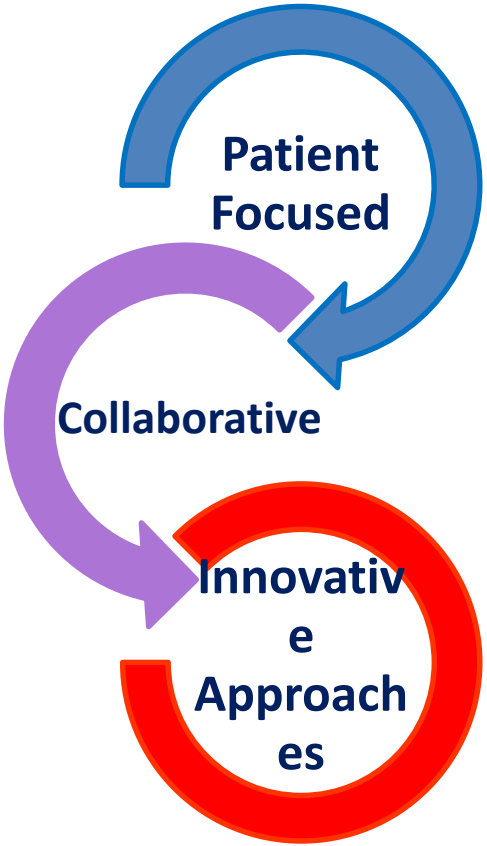

FDLI's Enforcement, Litigation and Compliance Conference

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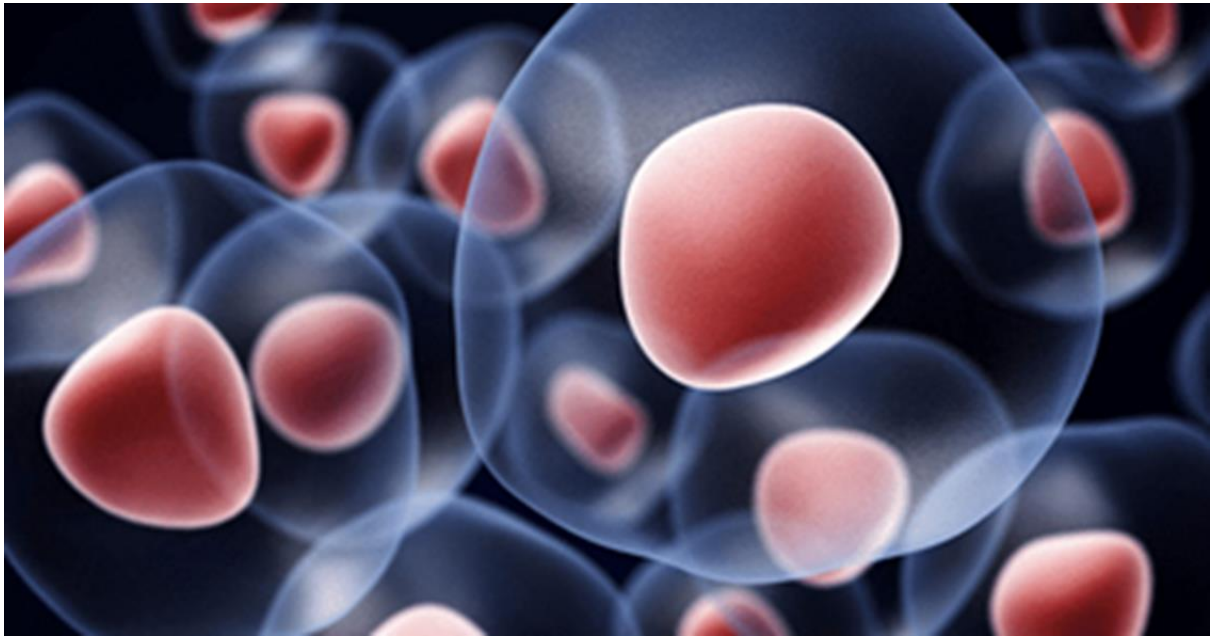
Center for Devices and Radiological Health
U.S. Food and Drug Administration

CBER Compliance Update
2018 FDLI Enforcement, Litigation, and Compliance Conference

Melissa J. Mendoza, J.D.
Deputy Director, Office of Compliance and Biologics Quality
Center for Biologics Evaluation and Research

Actions Involving Purported Stem Cell Products



StemGenex Biologic Laboratories, LLC

- WL issued October 31, 2018, following FDA inspection
- Autologous stromal vascular fraction product
- High-risk routes of administration
- Intended to treat a variety of diseases and conditions: Alzheimer's disease, Crohn's disease, diabetes, fibromyalgia, spinal cord injury, COPD, MS . . .
- Product regulated as a drug & biological product
- No BLA, NDA, or IND; CGMP violations documented

Mid America Stem Cell Institute

- UL issued July 17, 2018
- Autologous SVF product
- High-risk routes of administration
- Marketed to help people suffering from a variety of inflammatory, autoimmune, and degenerative conditions
- “Conditions treated” included Lupus, Crohn’s disease, RA, MS, ALS, spinal cord injury, COPD, allergies . . .
- No BLA, NDA, or IND

Recent Litigation, Enforcement, or Compliance Actions

- **Two Pending Actions for Permanent Injunction**
  - *United States v. US Stem Cell Clinic, LLC et al.* (S.D. Fla.)
  - *United States v. California Stem Cell Treatment Center, Inc. et al.* (C.D. Cal.)
- **ACAM2000, Vaccinia Virus Vaccine Seizure**
  - Default Judgment of Forfeiture filed 03/20/18 (C.D. Cal.)
- **Other Recent Warning Letters**
  - American Cryostem 01/03/18; US Stem Cell Clinic 08/24/17; RTI Surgical, Inc. 11/08/17

Going Forward

- Ongoing litigation
- Compliance and Enforcement Policy Regarding Certain Regulatory Requirements
  - https://www.fda.gov/biologicsbloodvaccines/guidancecompliance regulatoryinformation/guidances/tissue/
- Continued coordination with agency and government partners
- Welcome complaints
- Stay tuned!

Actions Involving Other CBER-Regulated Products

Diverse Range of Untitled Letters

- **Allergenics**
  - www.ollereg.com (10/11/18)
- **Plasma Derivatives**
  - CSL Behring, LLC (02/27/18)
- **Vaccines**
  - MassBiologics (10/02/18)
- **HIV Test Kits**
  - Not approved/cleared
    - www.stdrapidtest.com
    - www.testhivstatus.com
    - www.testkitlabs.com
    - www.testkitmart.com (7/27/18)
  - Restricted device sold and distributed not in accordance with approval/regulations
    - Tiger Medical, Inc. (05/29/18)
- **PRP Kits**
  - Physicians Products, Inc. (01/26/18)
  - Ycellbio Medical Co., Ltd. (07/10/18)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ORA Compliance Central

Ellen Morrison
Assistant Commissioner for Medical Products and Tobacco Operations
Office of Regulatory Affairs, FDA

ORA Agenda

- Program Alignment
  - Upcoming device initiatives
  - BIMO updates
  - Biologic updates
  - Pharma trends
- Mutual Reliance

Pharma Warning Letters

FY 2017

- International - 52
- Domestic - 15

FY 2018

- International – 75
- Domestic - 19

Pharma Industry Receiving WL

Drug Type Manufactured	FY2017	FY2018
FDF	21	20
API	3	2
Both	43	71
PET	0	1
Total	67	94

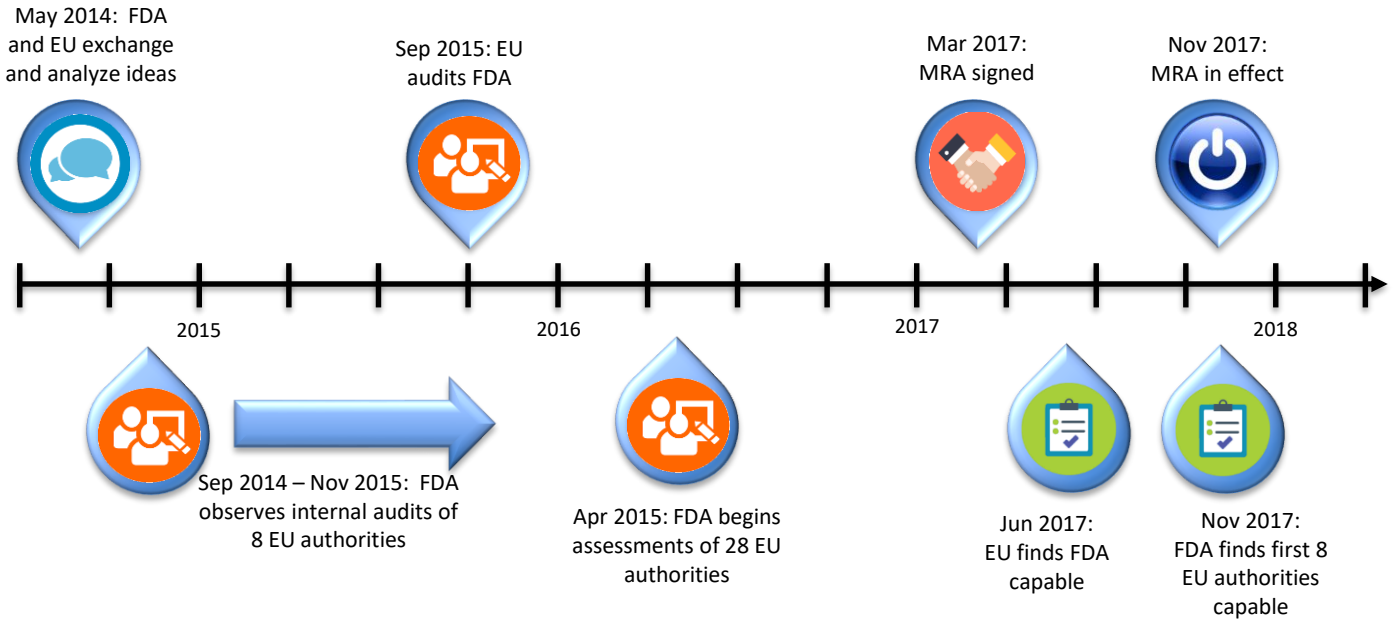
Top citations FY 2017

Violation	Count
211.192 - Complaint investigations.	15
211.100(a) - Validated production and process controls.	13
211.113(b) - Control of microbiological contamination (sterile).	11
211.165(a) - Failure to test finished products.	10
211.160(b) - Lack of established lab controls.	10
211.84(d)(1) and (2) - Components tested for identity and conformity with specifications.	7
211.22(d) - Written procedures for responsibilities of quality unit.	7
211.67(a) - Equipment cleaning and maintenance.	6
211.22(a) - Responsibilities of quality unit.	6
211.194(a) - Laboratory records include complete data.	5

Top citations FY 2018

Violation	Count
211.84(d)(1) and (2) - Components tested for identity and conformity with specifications.	28
211.100(a) - Validated production and process controls.	26
211.192 - Complaint investigations.	21
211.165(a) - Failure to test finished products.	19
211.22(a) - Responsibilities of quality unit.	17
211.166(a) - Inadequate stability testing.	15
211.194(a) - Laboratory records include complete data.	11
211.22(a) and (d) - Responsibilities of quality unit; written procedures.	10
211.67(b) - Written procedures for equipment cleaning and maintenance. / 211.165(a) and (b) - Failure to test finished products, including for microorganisms. / 211.137(a) - Expiration dating determined by appropriate stability testing.	8
211.42(c) - Separate areas to prevent contamination or mix-ups. / 211.22(d) - Written procedures for responsibilities of quality unit. / 211.160(b) - Lack of established lab controls.	6

Mutual Recognition Agreement



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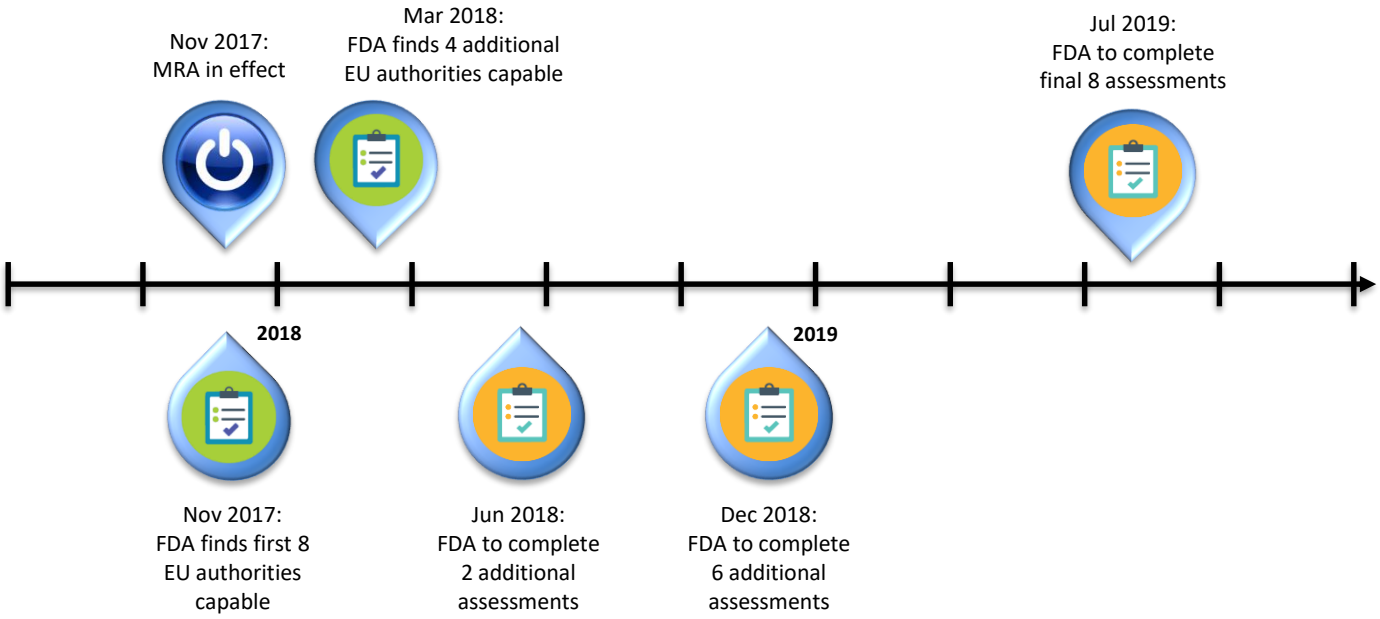


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