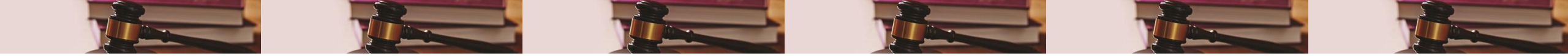

Compliance Central with FDA Center Compliance Directors: Part I

Donald Ashley, Director, Office of Compliance, Center for Drug Evaluation and Research, FDA

Erin Keith, Associate Director for Compliance and Quality, Center for Devices and Radiological Health, FDA

Melissa Mendoza, Deputy Director, Office of Compliance and Biologics Quality, Center for Biologics Evaluation and Research, FDA

Moderated by **Thomas J. Cosgrove**, Partner, Covington & Burling LLP

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U.S. FOOD & DRUG ADMINISTRATION

Compliance Central with FDA CDER Compliance Director

Donald D. Ashley, J.D.

Enforcement, Litigation and Compliance Conference
December 11, 2019

Strategic Areas

- Promote compliance
- Risk-based regulatory and enforcement actions
- Operational excellence

Concept of Operations

Goal: Create and implement a formalized and streamlined facility evaluation and inspection program

90-day Classification Letter

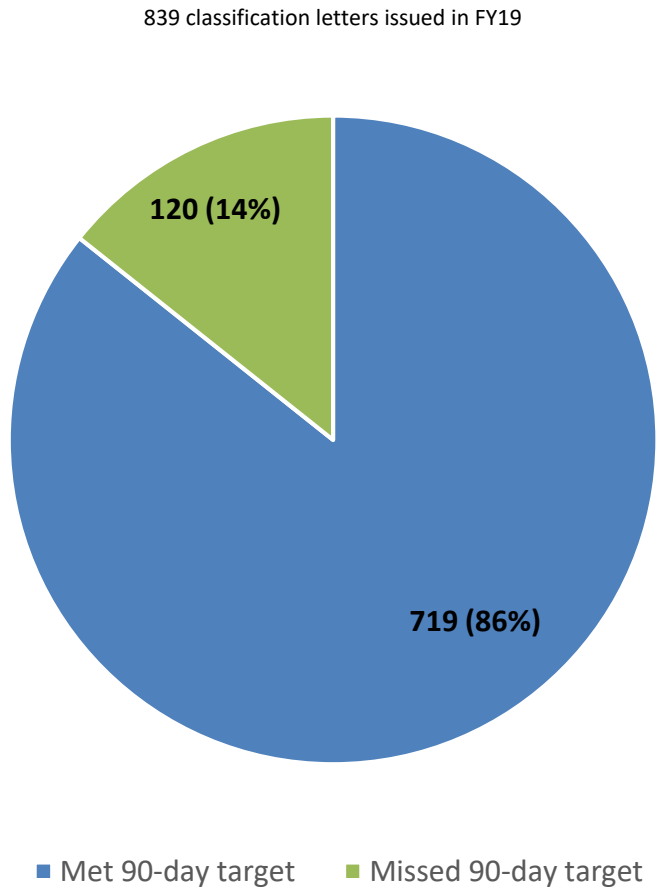
- Rate of classification letters issued by FDA in 90 days from close of inspection

OAI Regulatory Actions

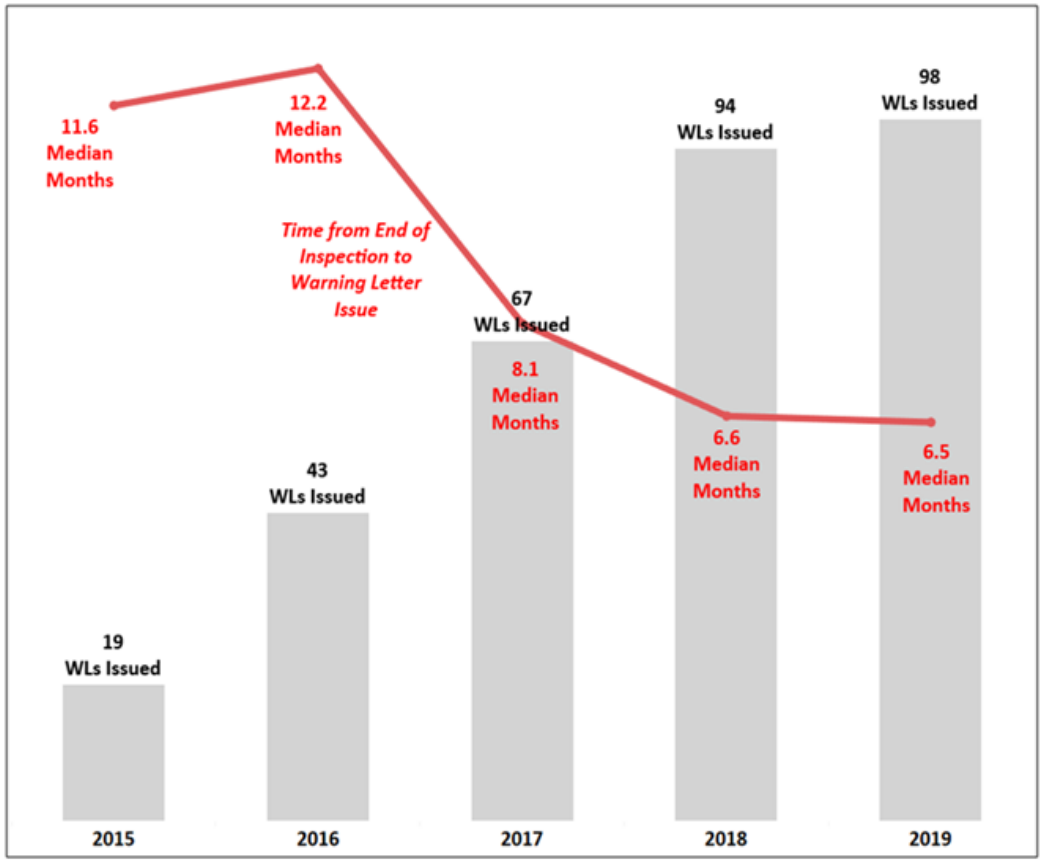
- Rate of OAI regulatory actions completed in 6 months from the closing of the inspection

Key Performance Indicators

90-day Classification Letters in FY 19



FY 2015-2019: Overall median 44% improvement in time to issue warning letters from the end of inspection



Total CGMP Warning Letters by Country: FY 2019

WARNING LETTER

Greenbrier International, Inc dba Dollar Tree

MARCS-CMS 574706 — NOVEMBER 06, 2019

"Considering that FDA has found a pattern of drug manufacturers with serious CGMP violations in your supply chain, in response to this letter, provide a detailed plan to ensure you do not receive or deliver adulterated drugs in interstate commerce, in violation of section 301 (c) of the FD&C Act, 21 U.S.C. 331(c)."

"You are responsible for ensuring that the drugs you distribute are manufactured in compliance with all relevant CGMP requirements for drugs. Up to date information regarding import alerts can be found at the following FDA website: https://www.accessdata.fda.gov/cms_ia/ialist.html."

"You are responsible for ensuring that the drugs you distribute are not adulterated, including ensuring that all drug manufacturers supplying Greenbrier with drugs have had release testing conducted in accordance with CGMP requirements."

- Excerpts from Greenbriar International Warning Letter

FDA NEWS RELEASE

FDA and DEA warn website operators illegally selling opioids

First-of-its-kind joint warning letters target 10 websites

September 6, 2019

"Today's effort is also noteworthy because while the FDA partners regularly with the DEA, this is the first time we have issued joint warning letters with them. This action further strengthens the warning to the operators of these websites…."

- Former Acting FDA Commissioner Ned Sharpless, M.D.

"Issuing these warning letters is not only an effort to deter the availability of dangerous illegal opioids, but it is also a testament to the close cooperation between DEA and FDA."

- Acting DEA Administrator, Uttam Dhillon

First DSCSA Warning Letter: McKesson Corporation

February 7, 2019

"McKesson did not sufficiently respond to the notification that they may have distributed illegitimate products."

"McKesson could not demonstrate that they took efforts to identify or quarantine additional illegitimate products that may have still been in their distribution facilities."

"[M]cKesson did not notify other pharmacy customers who may have received products with the same lot number or National Drug Code to make them aware of potential illegitimate product in the supply chain."

- Former FDA Commissioner Scott Gottlieb, M.D.

FDA NEWS RELEASE

FDA warns 15 companies for illegally selling various products containing cannabidiol as agency details safety concerns

Violations include marketing unapproved new human and animal drugs, selling CBD products as dietary supplements, and adding CBD to human, animal foods

Compounding Injunctions FY 2019

Federal court enters consent decree against Ranier's Rx Laboratory and owner for manufacturing purportedly sterile drug products in insanitary conditions

- *FDA News Release February 6, 2019*

Federal Judge enters consent decree against Texas compounder, Guardian Pharmacy Services

- FDA News Release March 12, 2019

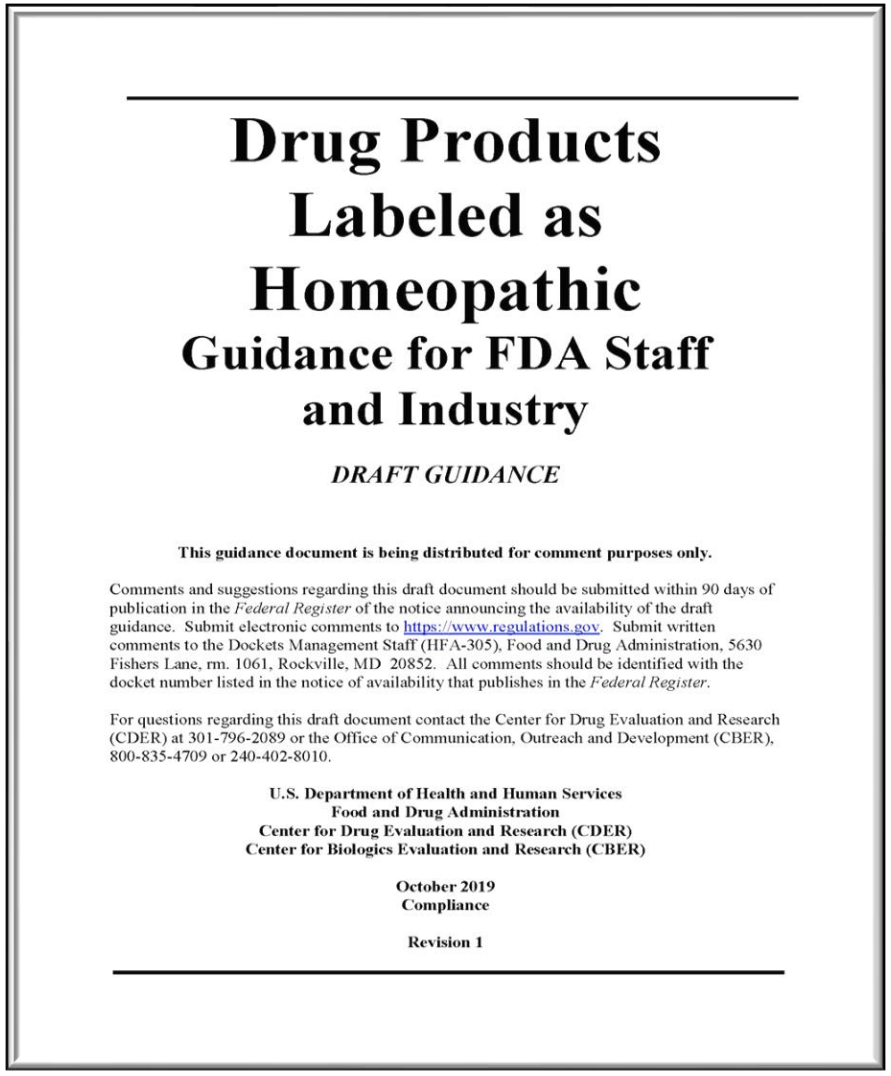
Federal court enters consent decree against Texas compounder, Pharm D Solutions, LLC to cease the manufacturing of drugs intended to be sterile due to insanitary conditions

- FDA News Release May 22, 2019

Federal judge enters consent decree against compounder PharMedium Services for violations at multiple facilities

- *FDA News Release May 22, 2019*

Homeopathic Drugs: A Risk-Based Approach to Enforcement



Drug Products Labeled as Homeopathic

Guidance for FDA Staff and Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

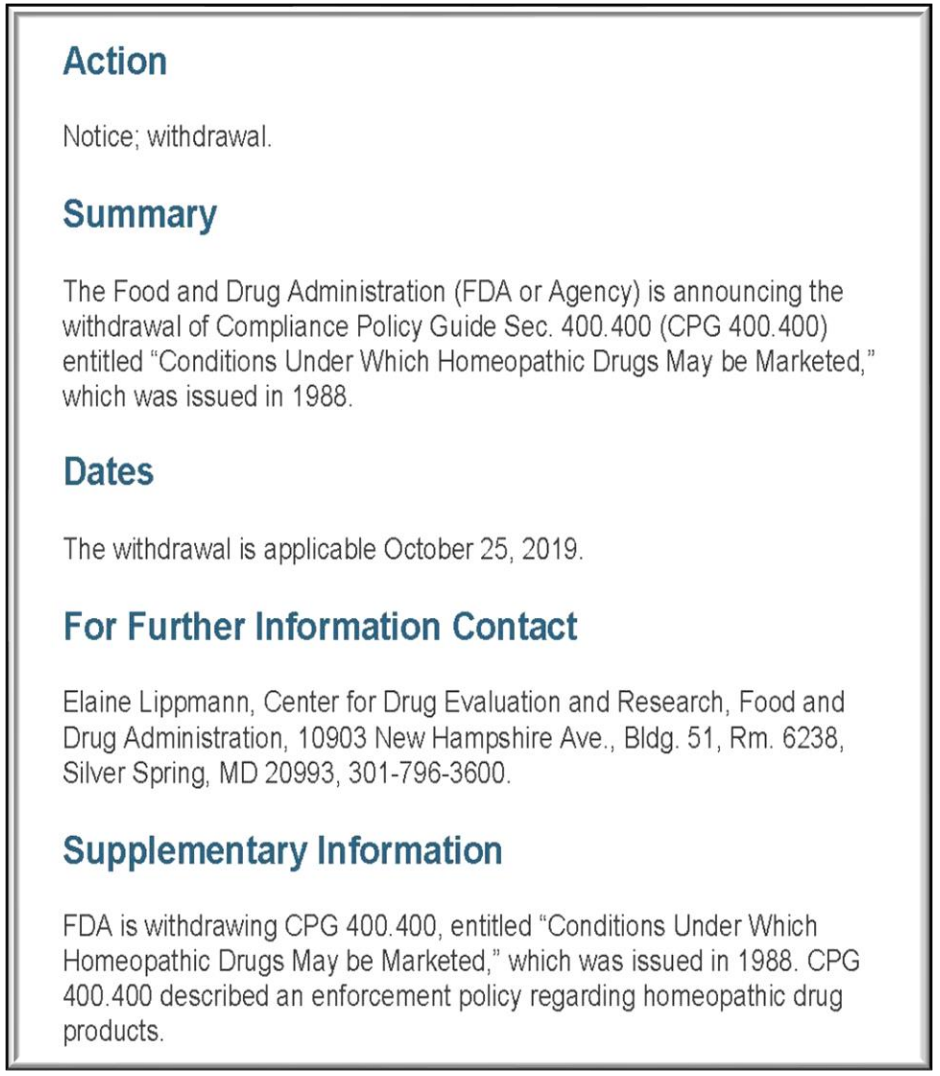
Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact the Center for Drug Evaluation and Research (CDER) at 301-796-2089 or the Office of Communication, Outreach and Development (CBER), 800-835-4709 or 240-402-8010.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

October 2019
Compliance

Revision 1



Action

Notice; withdrawal.

Summary

The Food and Drug Administration (FDA or Agency) is announcing the withdrawal of Compliance Policy Guide Sec. 400.400 (CPG 400.400) entitled "Conditions Under Which Homeopathic Drugs May be Marketed," which was issued in 1988.

Dates

The withdrawal is applicable October 25, 2019.

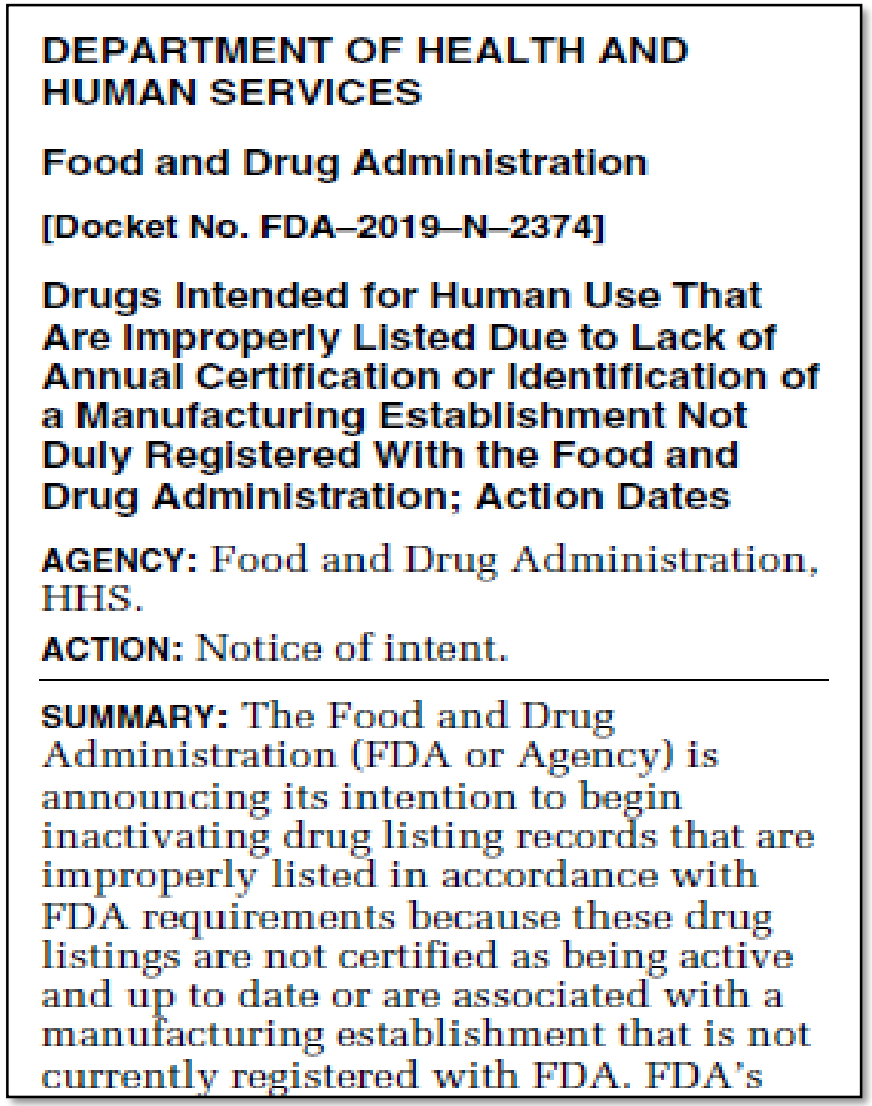
For Further Information Contact

Elaine Lippmann, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, Rm. 6238, Silver Spring, MD 20993, 301-796-3600.

Supplementary Information

FDA is withdrawing CPG 400.400, entitled "Conditions Under Which Homeopathic Drugs May be Marketed," which was issued in 1988. CPG 400.400 described an enforcement policy regarding homeopathic drug products.

eDRLS Inactivation



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA–2019–N–2374]

Drugs Intended for Human Use That Are Improperly Listed Due to Lack of Annual Certification or Identification of a Manufacturing Establishment Not Duly Registered With the Food and Drug Administration; Action Dates

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice of intent.

SUMMARY: The Food and Drug Administration (FDA or Agency) is announcing its intention to begin inactivating drug listing records that are improperly listed in accordance with FDA requirements because these drug listings are not certified as being active and up to date or are associated with a manufacturing establishment that is not currently registered with FDA. FDA's

As of mid-November, eDRLS has inactivated over 15,200 NDCs belonging to firms that are no longer registered or no longer marketing the particular drug products

Center of Excellence

- Congress appropriated funds for FDA to create a “Compounding Quality Center of Excellence.”

- Goals:
  - Enhance engagement with outsourcing facilities
  - Bolster the quality of compounded drugs
  - Encourage adherence to higher quality standards to protect patient health


COMPLIANCE


FDA
U.S. FOOD & DRUG
ADMINISTRATION

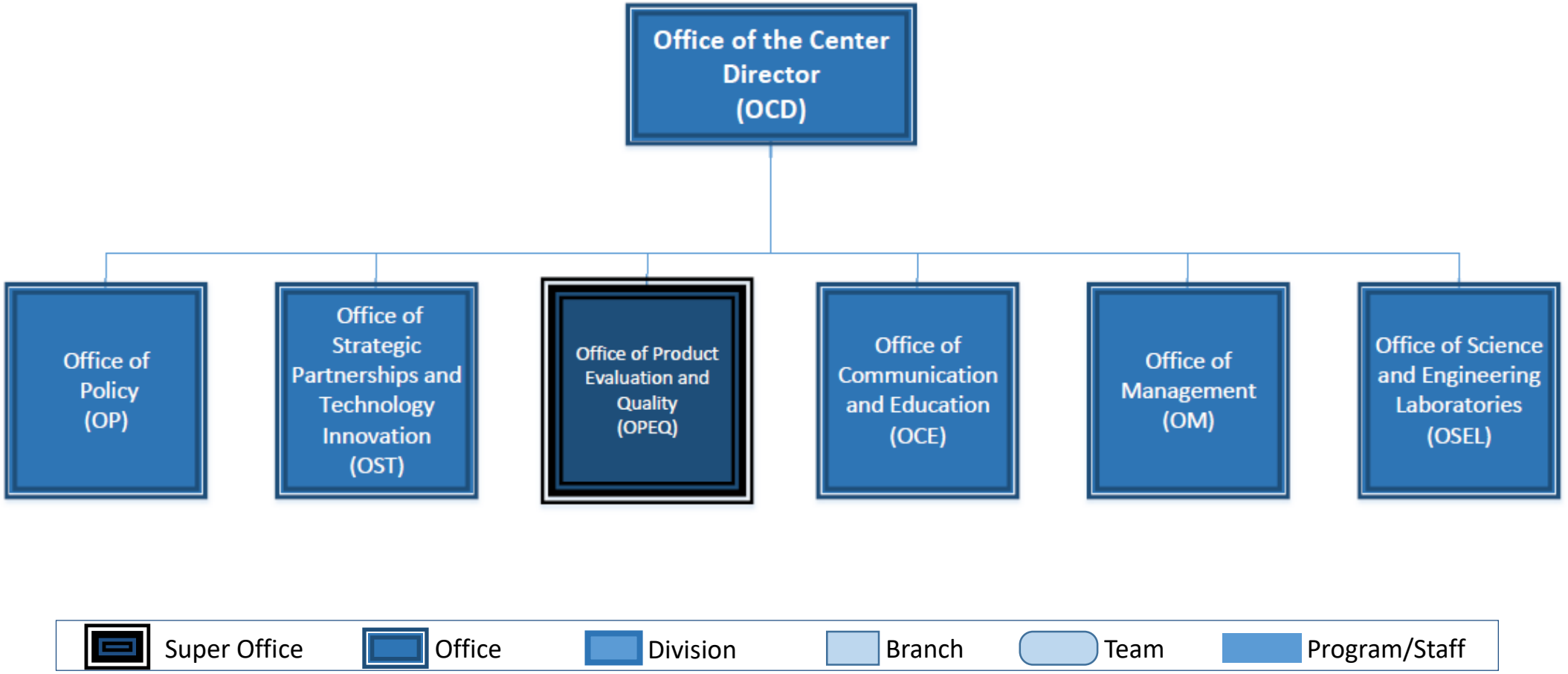
Compliance and Quality

Office of Product Evaluation and Quality

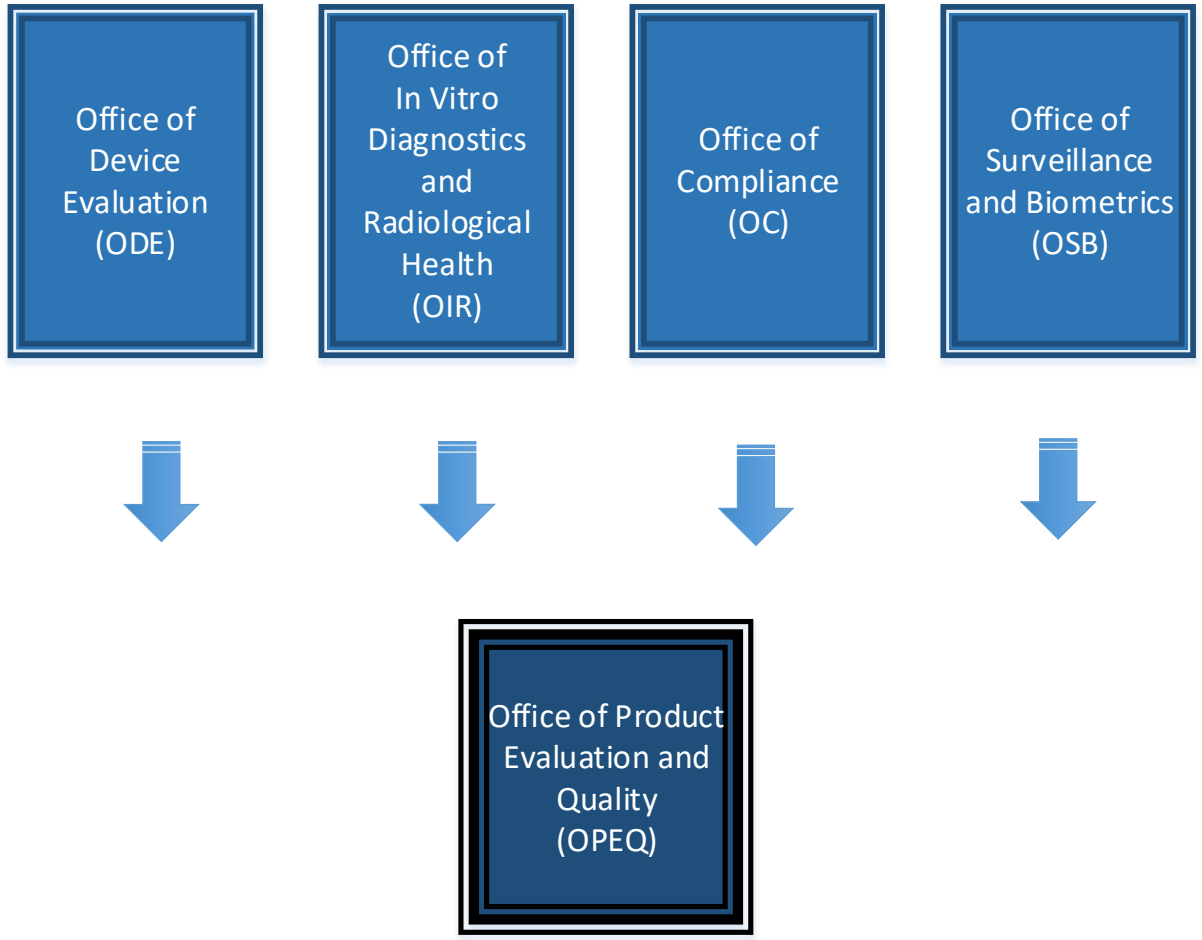
CDRH

Erin Keith
OPEQ Associate Director, Compliance and Quality

New CDRH Structure After Reorg Implementation

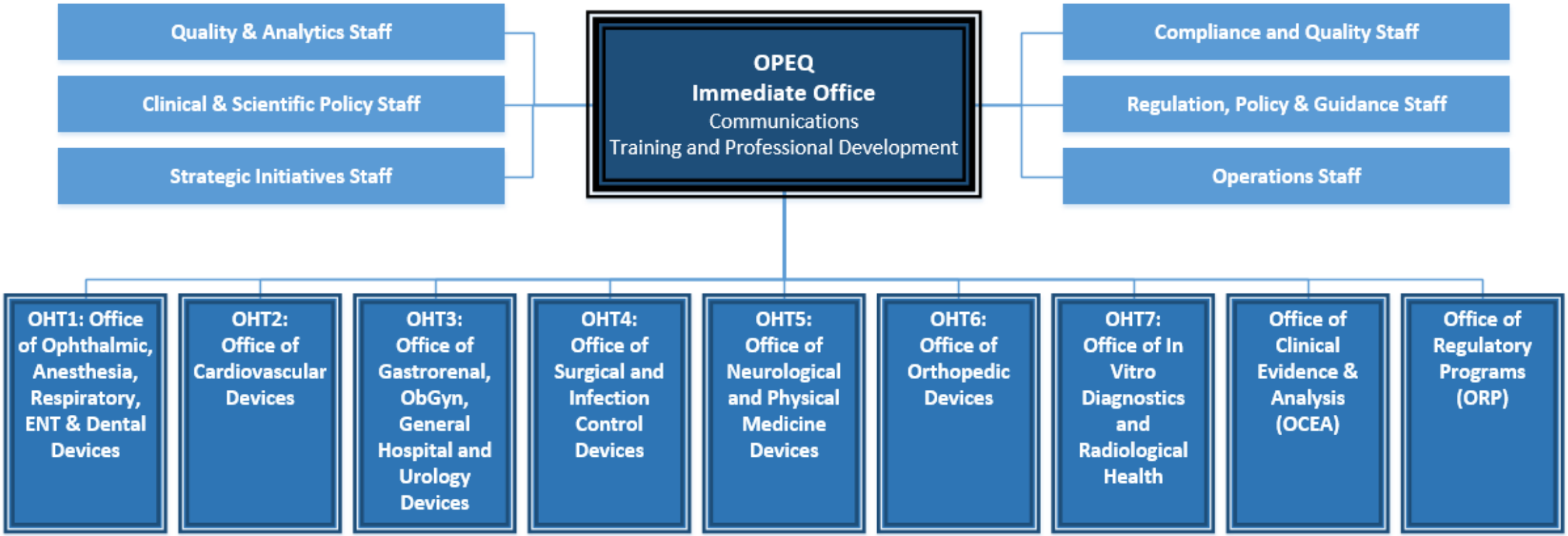


Office of Product Evaluation and Quality



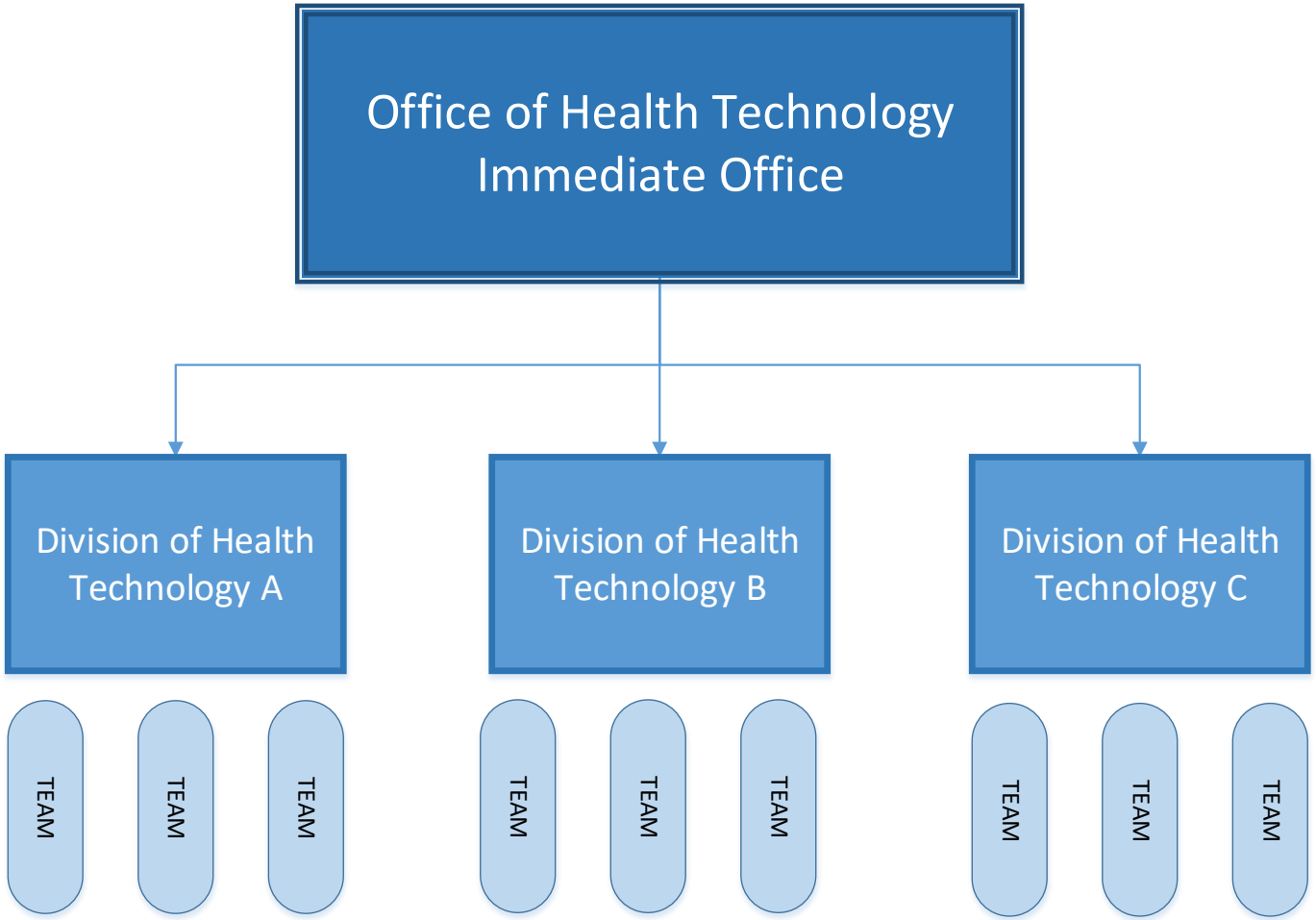
- OC, ODE, OIR and OSB reorganized into one Super Office (OPEQ)
- OPEQ has 9 offices

Office of Product Evaluation and Quality

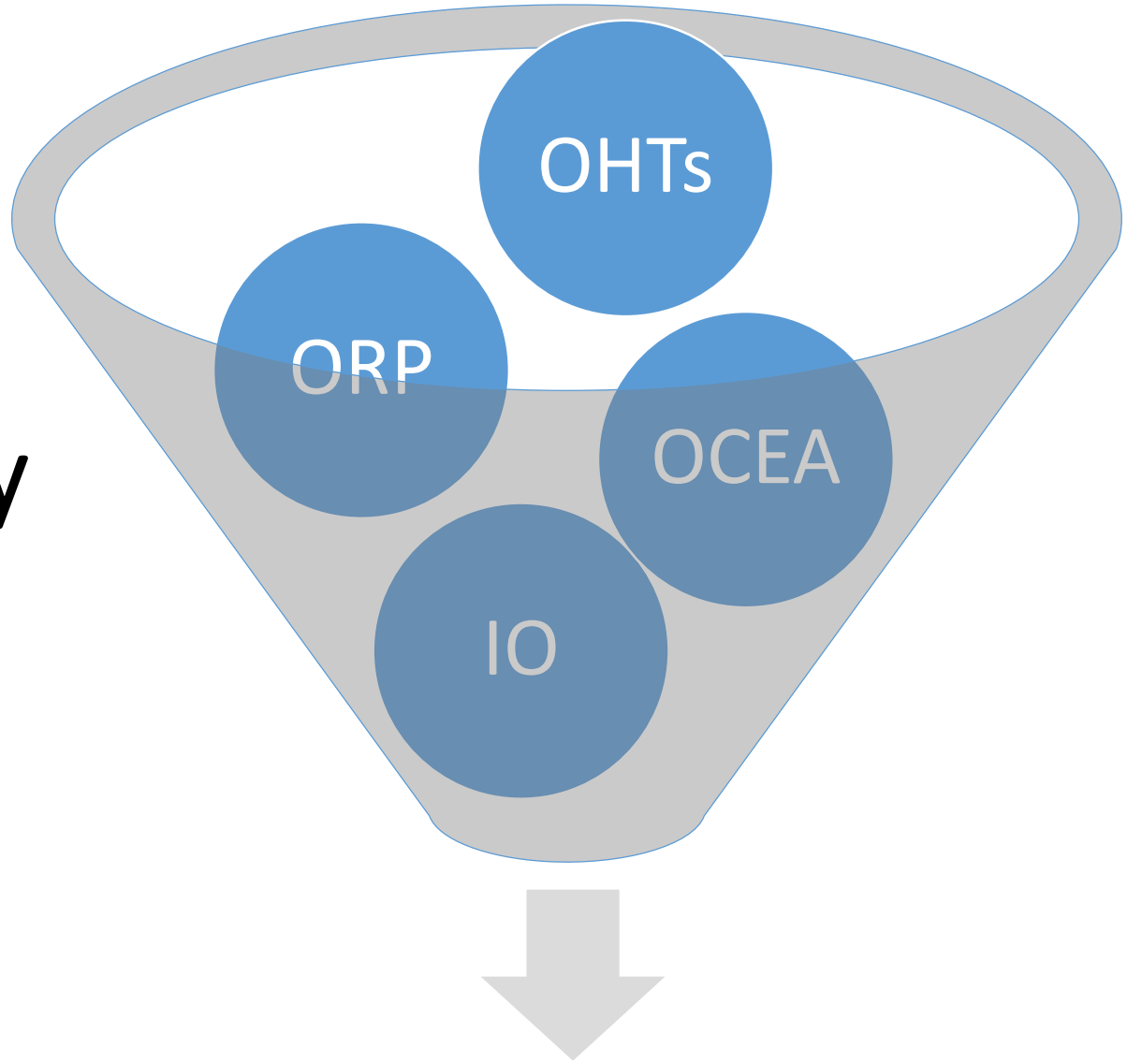


OHT= Office of Health Technology

Generic Office of Health Technology (OHT)



Compliance and Quality Programs in OPEQ



OPEQ Compliance and Quality Program Contacts

OPEQ Organization	Name/Title	Email	Responsibilities
Immediate Office	Erin Keith Associate Director for Compliance and Quality	Erin.Keith@fda.hhs.gov	Compliance and Quality Programs
Immediate Office	Patrick Weixel Acting Senior Advisor	Patrick.Weixel@fda.hhs.gov	Compliance and Enforcement Strategy
Immediate Office	Francisco Vicenty CfQ Program Manager	Francisco.Vicenty@fda.hhs.gov	Case for Quality
ORP	Sean Boyd Director	Sean.Boyd@fda.hhs.gov	Compliance Regulatory Programs
ORP/DRP1	Joshua Nipper Director	Joshua.Nipper@fda.hhs.gov	Submission Support Programs (PMA, HDE, 510k, Denovo, etc.)
ORP/DRP2	Cesar Perez Director	Cesar.Perez@fda.hhs.gov	Establishment Support Programs (Inspections, Audits, Imports, R&L, Exports)
ORP/DRP3	Donna Engelman Director	Donna.Engleman@fda.hhs.gov	Market Intelligence Programs (Recall, Shortages, Allegations and MDRs)

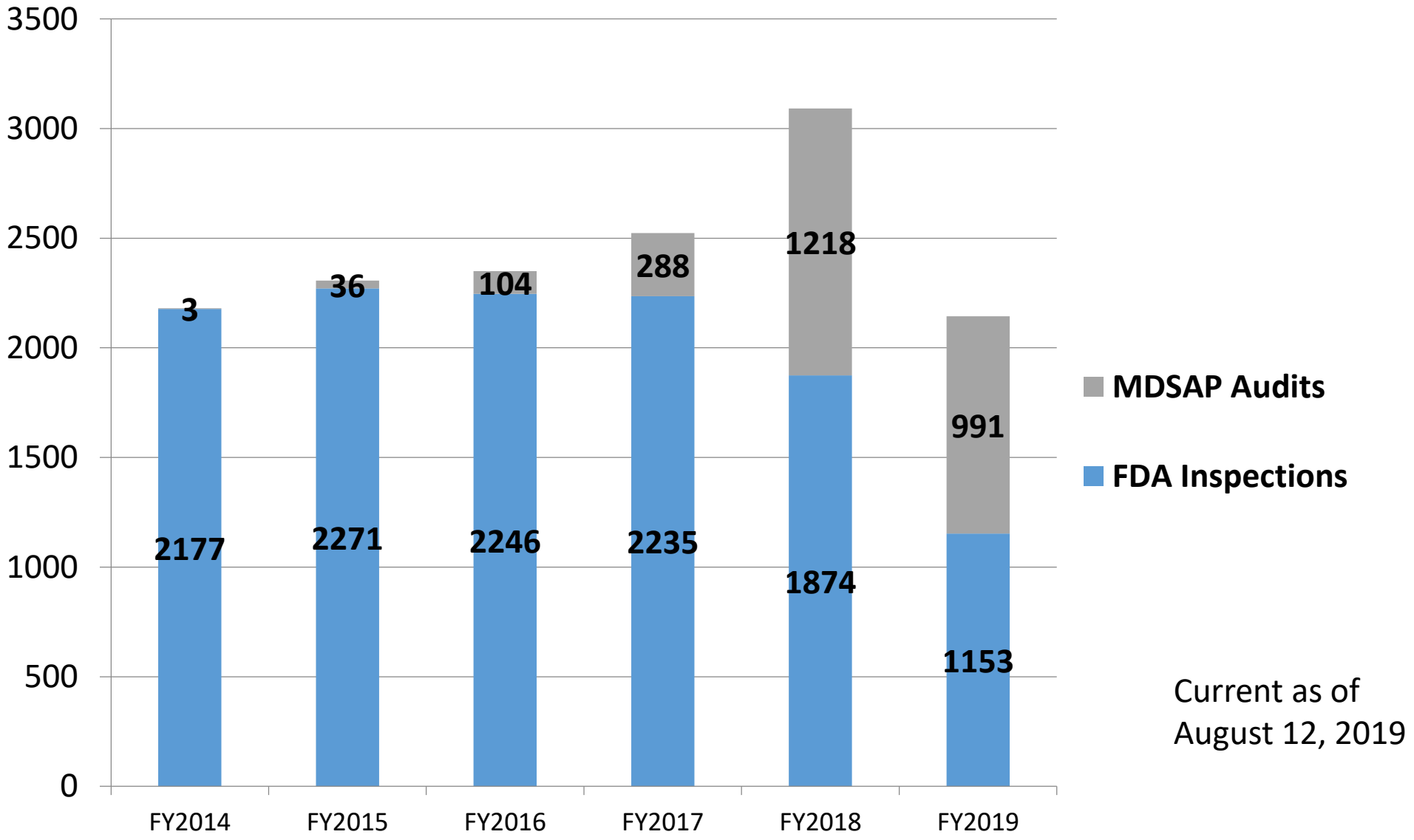
OPEQ Compliance and Quality Program Contacts

OPEQ Organization	Name/Title	Email	Responsibilities
OCEA/DCEA1	Adam Donat Deputy Director	Adam.Donat@fda.hhs.gov	BIMO Programs
OHT1	Keisha Thomas Deputy Director	Keisha.Thomas@fda.hhs.gov	OHT1 Compliance Lead
OHT2	William MacFarland Deputy Director	William.MacFarland@fda.hhs.gov	OHT2 Compliance Lead
OHT3	Ann Ferriter Associate Director	Ann.Ferriter@fda.hhs.gov	OHT3 Compliance Lead
OHT4	Jennifer Stevenson Deputy Director	Jennifer.Stevenson@fda.hhs.gov	OHT4 Compliance Lead
OHT5	Nina Mezu-Nwaba Acting Deputy Director	Nina.Nwaba@fda.hhs.gov	OHT5 Compliance Lead
OHT6	Raquel Peat Director	Raquel.Peat@fda.hhs.gov	OHT6 Compliance Lead
OHT7	Courtney Lias Acting Deputy Director	Courtney.Lias@fda.hhs.gov	OHT7 IVD Compliance Lead
OHT7/DRH	David Dar Acting Deputy Director	David.Dar@fda.hhs.gov	OHT7 Rad Health Compliance Lead

OPEQ Compliance and Quality Programs: Key Shifts in Focus

- Total Product Lifecycle Regulatory Approach
- Harmonization
- Voluntary Quality Improvement Programs

Medical Device QS Surveillance Inspections and MDSAP Audits



Current as of August 12, 2019

ISO 13485 and the FDA Quality System Regulation

- 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.

See Unified Agenda: Harmonizing and Modernizing Regulation of Medical Device Quality Systems

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

- ✓ **23** participating firms
- ✓ **>40** appraisals
- ✓ **86%** report appraisal had a positive impact on product quality

Case for Quality

Launched by the CDRH to address risks to patients by transitioning industry and the medical device ecosystem to a culture that prioritizes product quality and patient outcomes

Collaborative effort facilitated by the Medical Device Innovation Consortium (MDIC) to engage all stakeholders in the ecosystem to identify, implement, and incentivize ways to improve patient safety and outcomes through high-quality medical devices

Voluntary Improvement Program

Voluntary pilot in which third party teams certified by the Capability Maturity Model Integration (CMMI) Institute conduct quality system maturity appraisals with the goal of driving continuous improvement and organizational excellence

Enhance Data and Analytics

Increase adoption of advanced product development technologies and practices

Increase use of objective performance metrics in oversight and decision making across ecosystem

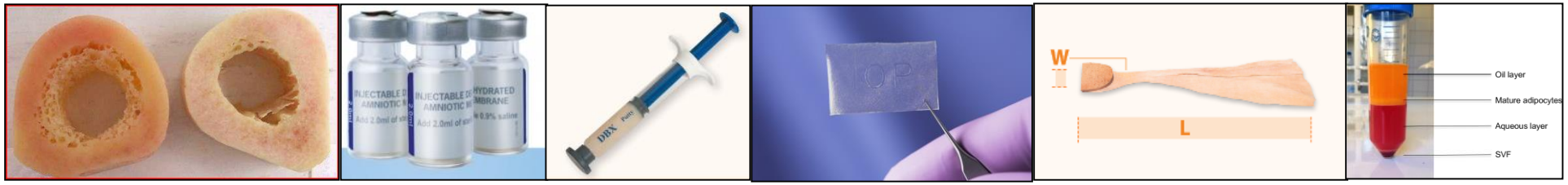
Adaptive Regulatory Framework

Modernize regulatory oversight to increase agility, responsiveness, simplification, error-proofing, and enable continuous rapid improvement

Accelerate safety and innovation

Questions

CBER Compliance and Enforcement Update



December 11, 2019

Melissa J. Mendoza, JD
Deputy Office Director
Office of Compliance and Biologics Quality
Center for Biologics Evaluation and Research
United States Food and Drug Administration

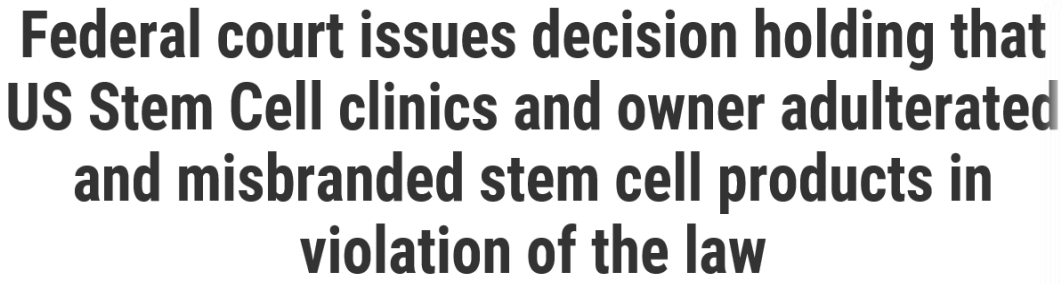
Injunction Entered:

United States v. US Stem Cell Clinic LLC et al. (S.D. Fla.)

Health

FDA wins groundbreaking case against for-profit stem cell company

FDA NEWS RELEASE



Federal court issues decision holding that US Stem Cell clinics and owner adulterated and misbranded stem cell products in violation of the law

F.D.A. Can Act Against Stem Cell Clinic, Judge Rules

A Florida judge says the agency is entitled to an injunction against a stem cell clinic that has blinded patients and challenged the government's authority to regulate it.

Los Angeles Times

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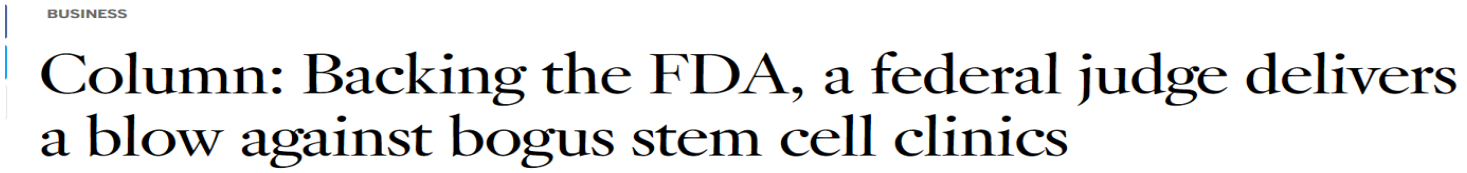


BUSINESS

Column: Backing the FDA, a federal judge delivers a blow against bogus stem cell clinics

Ongoing Enforcement Action: *United States v. California Stem Cell Treatment Center, Inc., Cell Surgical Network Corporation, et al.* (C.D. Cal.)

- Permanent injunction sought against California Stem Cell Treatment Center, Inc., Cell Surgical Network Corporation, and Elliot B. Lander, MD and Mark Berman, MD
- Defendants' SVF products used to treat a variety of serious diseases or conditions, including cancer, arthritis, stroke, ALS, MS, macular degeneration, Parkinson's disease, and COPD
- Products not approved for any use

Recent Cases Follow:

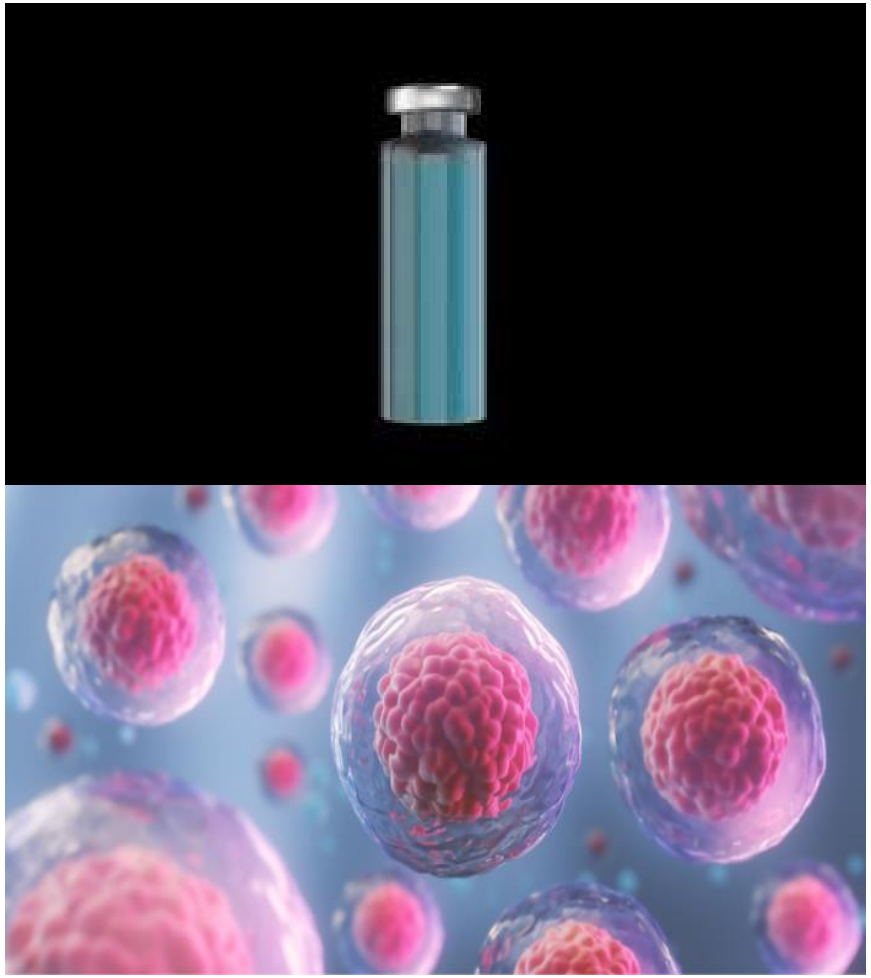
- *United States v. Five Articles of Drug, ACAM 2000, Vaccinia Virus Vaccine, Live*, No. 17-11448 (C.D. Cal. Mar. 20, 2018)
- *United States v. Regenerative Sciences LLC*, 741 F.3d 1314 (D.C. Cir. 2014)

What's New?

Products From:

- Umbilical cord blood
- Umbilical cord tissue
- Adipose tissue (fat)
- Amniotic Fluid*
- Multiple Sources Combined

Now Featuring:
EXOSOMES !



Compliance Snapshot
November – December 2019

RICHSOURCE®
STEM CELLS, INC

CHARA
BIOLOGICS, INC

Warning Letter to Liveyon Labs, Inc. and Liveyon LLC – December 6

- Unlawfully processing and distributing unapproved products derived from umbilical cord blood
- https://www.fda.gov/news-events/press-announcements/fda-sends-warning-companies-offering-unapproved-umbilical-cord-blood-products-may-put-patients-risk

Public Safety Notification – December 6

- On exosome products
- Reports of serious adverse events
- https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/public-safety-notification-exosome-products

Order to Cease Manufacturing – November 27

- CBER ordered Gynecology, Reproductive Endocrinology and Fertility Institute of Puerto Rico to cease manufacturing immediately
- Significant donor eligibility violations, including donor screening and testing
- Posed danger to health
- https://www.fda.gov/news-events/press-announcements/fda-orders-puerto-rico-fertility-clinic-cease-manufacturing-immediately-significant-violations-pose

Untitled Letter to Chara Biologics, Inc. – November 26

- "[U]mbilical, cord tissue and amniotic membrane" product
- Marketed to parents of children with autism and young adults suffering from traumatic brain injury
- "Suitable for all forms of injection, to assist the body's ability to repair and regenerate"
- Not approved for any use

Untitled Letter to RichSource Stem Cells, Inc. – November 20

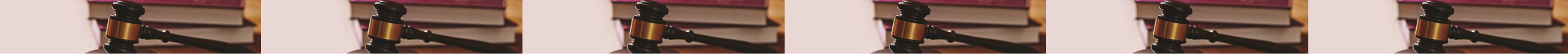
- Product described as a combination of amniotic fluid and membrane, Wharton's jelly, and placental tissue
- Claimed to treat cancer, tumors, diabetes, Lyme's disease, asthma, COPD, various orthopedic conditions, and "topical wound healing"
- Not approved for any use

“It’s Come to Our Attention” Letters

- Over 20 Issued in November
- Brings total to over 80 issued since December 2018

Thank you!
Questions/Comments?

Contact Info:
Melissa.Mendoza@fda.hhs.gov



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