Center for Drug Evaluation and Research (CDER)

Janet Woodcock, Director, Center for Drug Evaluation and Research, FDA
Jeff Allen, President & CEO, Friends of Cancer Research
Dave Ceryak, Senior Director, Assistant General Counsel, Regulatory Legal Team, Eli Lilly and Company
Philip Katz, Partner, Hogan Lovells US LLP
Christine Simmon, Senior Vice President, Policy & Strategic Alliances, Association for Accessible Medicines
Moderated by **Deborah M. Shelton**, Partner, McCarter & English LLP

CDER UPDATE

Janet Woodcock

Director, CDER, FDA

New Drugs Regulatory Program Modernization

New Drugs Regulatory Program Modernization: Overall Objectives

Objectives	Guiding principles for modernizing the new drugs regulatory program
Scientific Leadership	**We will grow our scientific expertise and clarify pathways to regulatory approval.** • Expanding the armamentarium to address unmet medical needs is an important part of our public health mission. • Towards that end, we will proactively collaborate with academic medical scientists and patient/disease advocates, evaluate scientific gaps, and strategically foster drug development.
Integrated Assessment	**We will critically, collaboratively and consistently assess whether information in submissions meets statutory and regulatory requirements.** • We will take a new approach to document our assessments, developing a more integrated, cross-disciplinary document to foster collaboration and reduce redundant information. • Our assessments will be rigorous, risk-based, and clinically relevant; focus on the key issues; and incorporate the patient perspective.
Benefit-Risk Monitoring	**We will establish a unified post-market safety surveillance framework.** • To effectively protect the American public, we will systematically monitor the benefits and risks of approved drugs across their lifecycles.
Managing Talent	**We will attract, develop, and retain outstanding people.** • We will use 21st Century Cures Act authorities to recruit and retain technical, scientific and professional experts, and eliminate our backlog of vacant positions.
Operational Excellence	**We will have a dedicated focus on operational excellence.** • We will enhance our ability to address OND's large volume workload through greater process standardization and better defined roles and responsibilities. • This will improve operational efficiency and enable our scientists to focus on science, not ancillary tasks.
Knowledge Management	**We will facilitate knowledge management.** • Vast and diverse information is submitted to and generated by the New Drugs Regulatory Program. • We will make it easy for our staff to find and use scientific and regulatory precedents. • This will reduce manual work time, increase the speed and efficiency of submission assessment, and increase the consistency and predictability of regulatory decision-making.

The New Drugs Regulatory Program has 6 active initiatives

Integrated Review for Marketing Applications	Developing a streamlined interdisciplinary review process and template to support the new integrated review for assessing NDA/BLAs
IND Review Management	Streamlining the IND scientific review processes for managing IND applications, beginning with 30-Day Safety Reviews and Protocols
Post-Market Safety Management	Creating a standardized, consistent, and effective approach to post-market drug safety
Assessing Talent	Developing an effective and consistent process for hiring, onboarding, developing and evaluating new Clinical and Pharm/Tox reviewers
Reorganization and Transition Management	Planning, coordinating, and implementing modernization and organization changes at the future Office and Division levels across the New Drugs Program
Administrative Operations	Optimize administrative and clerical staff roles, structure, and functions to enhance customer focus and employee engagement

Integrated Review of Marketing Applications

- Designing a streamlined issue-based integrated review process and template that results in an integrated FDA assessment, by
  - Creating **a template and a process** that are issue-based, foster interdisciplinary collaboration, reduce redundancy and low-value work, and enable better knowledge management
  - Developing a **tracking tool** to be utilized from pre-NDA through end of review cycle, allowing for systematic tracking of review issues for the entire review team
  - Adding **new roles** to allow reviewers to focus on the science and regulatory aspects of the application: (1) Clinical Data Scientists to support safety analysis and (2) Medical Editors to provide editing and formatting services
  - Incorporating **purposeful scoping working meetings** with early involvement of leadership to discuss known benefit and risk issues; and **joint assessment meetings** focused on specific review issues

Currently in Phased Implementation. All divisions to begin using the new process and template in 2020.

IND Review Management

- Addresses variable practices across divisions and reduces redundant documentation practices
- Creating templates that are **issue-based**, foster **interdisciplinary collaboration**, **reduce redundancy** and low-value work, and enable better **knowledge management**
- Establishing procedures that **standardize** the review process, clearly **define roles and responsibilities** and improve our ability to provide **high-quality feedback** to sponsors in a **timely manner**
- Developing a risk based approach to **categorize** incoming protocols and amendments and identify the protocols that should follow a **higher priority process** to review more expeditiously

Anticipate beginning implementation this summer

Post-Market Safety Management

Creates a **standardized** post-market drug safety framework that will include:

- **Cross-disciplinary, collaborative, science-focused** assessments
- Clear **roles, responsibilities,** and **governance**
- IT-enabled processes to enhance **knowledge management** and fit-for-purpose **analytic tools** to promote optimal evaluations
- **Policies and processes** (i.e., via SOPs, charters, templates) that support this framework

Anticipate beginning implementation this fall

Other Innovations Ongoing

- Biomarker, COA, and PRO qualification program (CURES)
- Model informed drug development (PDUFA)
- Innovative designs (PDUFA)
- Real world evidence program (CURES)
- Breakthrough therapy program
- Policy development on personalized medicine
- Patient focused drug development

Generic Drug Program

Recent Activity and Accomplishments

- Approved or tentatively approved 1,021 Abbreviated New Drug Applications (ANDAs) in 2018; issued 2,648 complete response letters detailing deficiencies
- Published more than 250 new or revised guidances, product-specific guidances (PSGs) and manuals of policies and procedures (MAPP) for stakeholders
- Successfully implemented many of the new provisions in GDUFA II and the FDA Reauthorization Act of 2017 (FDARA), including:
  - Pre-ANDA program, requests for reconsideration, and the Pre-submission Facility Correspondence program
  - One-time marketing status updates to the “Orange Book”
  - Competitive generic therapy designation and exclusivity requests

Activities and Accomplishments (cont.)

- Created dynamic communication processes that allow for more transparency and predictability for industry
- Launched a new online functionality for controlled correspondence inquiries from industry and responded to about 700 such inquiries via the Center for Drug Evaluation and Research's Direct NextGen Collaboration Portal

Drug Competition Action Plan (DCAP) Recent Activity

DCAP foundational goals:

- **Streamline ANDA review** process to increase efficiency, effectiveness, and output of approvals
- **Maximize scientific and regulatory clarity** with respect to generic drugs for **complex products**
- **Close loopholes** that allow brand drug companies to "game" the system in ways that thwart generic competition

Streamlining ANDAs

- Draft guidances on:
  - *Designation, Submission, and Review of ANDAs for Competitive Generic Therapies* (Feb. 2019)
  - *CDER's Program for the Recognition of Voluntary Consensus Standards Related to Pharmaceutical Quality* (Feb. 2019)
  - *ANDA Submissions – Requesting Final Approval of a Tentatively Approved ANDA* (Jan. 2019)
- Continued efforts on harmonizing scientific and technical standards for generic drugs under the International Council for Harmonisation (ICH)
  - ICH Assembly endorsed FDA's reflection paper describing the proposal (Nov. 2018)

Maximizing Scientific and Regulatory Clarity for Complex Generic Drug Products

- Issued 76 PSGs for complex generics in 2018
- Published multiple general guidances for industry, including:
  - Revised Draft Guidance on *Assessing Adhesion for ANDAs with Transdermal Delivery Systems and Topical Patches* (Oct. 2018)
  - Draft Guidance on *Assessing Irritation and Sensitization Potentials of Generic Transdermal and Topical Patches Submitted in ANDAs* (Oct. 2018)
- Conducted extensive public outreach

Closing Loopholes that Allow Brand Drug Companies to "Game" the System

- Semi-annually update list of drug product about which FDA has received inquiries related to reference listed drug access (most recently Dec. 2018)
- Draft guidance on *Citizen Petitions and Petitions for Stay of Action Subject to Section 505(q) of the Federal Food, Drug, and Cosmetic Act* (Oct. 2018)
- Draft guidances on *Development of a Shared System; Waivers of the Single Shared System REMS* (June 2018)
- *MAPP 6701.3 Development of a Single Shared System or a Separate Risk Evaluation and Mitigation Strategy with Elements to Assure Safe Use: Responsibilities and Procedures* (Feb. 2019)

Future Efforts

- Full speed ahead on implementing GDUFA II and the DCAP, including:
  - Continue extensive GDUFA and complex generic guidance activity, enhancing program review efficiency
  - Issue guidances on Orange Book, therapeutic equivalence, and Hatch-Waxman exclusivity; solicit stakeholder feedback to maximize utility of the Orange Book
  - Continue to work with international partners on harmonization efforts to facilitate faster development programs

Biosimilars Program

Development-Stage Advice to Sponsors

As of April 2, 2019:

- **77 programs (for 36 different reference products)** were enrolled in the **Biosimilar Product Development (BPD) Program** to discuss development of proposed biosimilar products or interchangeable products

Biosimilars Approved by FDA

As of April 2, 2019:

- **18** 351(k) BLAs for biosimilar products have been approved for 9 reference products.
  - **8** biosimilar products are believed to have been commercially launched

- **28 planned 351(k) submissions (from 16 companies)** have been publicly announced

FDA's Biosimilars Action Plan

Biosimilars Action Plan (BAP) provides information about key actions the Agency is taking to encourage innovation and competition among biologics and the development of biosimilars.

1. Improving the efficiency of the biosimilar and interchangeable product development and approval process
2. Maximizing scientific and regulatory clarity for the biosimilar product development community
3. Developing effective communications to improve understanding of biosimilars among patients, clinicians and payors
4. Supporting market competition by reducing gaming of FDA requirements or other attempts to unfairly delay competition

BAP Deliverables

Completed

Completed	*Deliverable*
December 2018	Questions and Answers on Biosimilar Development and the BPCI Act; Final Guidance
December 2018	New and Revised Draft Q&As on Biosimilar Development and the BPCI Act (Revision 2); Draft Guidance
December 2018	Interpretation of the Deemed to be a License Provision of the Biologics Price Competition and Innovation Act; Final Guidance
December 2018	The Deemed to be a License Provision of the BPCI Act: Questions and Answers; Draft Guidance
December 2018	Definition of the Term Biological Product; Proposed Rule
December 2018	Preliminary List of Approved NDAs for Biological Products That Will Be Deemed to be BLAs on March 23, 2020
March 2019	Nonproprietary Naming of Biological Products – Update; Draft Guidance

Selected Forthcoming BAP Deliverables

BAP Goal	*Deliverable*
Goal 2	Considerations in Demonstrating Interchangeability with a Reference Product; Final Guidance (user fee goal date of May 17, 2019)
	Revised draft guidance on comparative analytical assessments (user fee goal date of May 21, 2019)
	Biosimilar and Interchangeable Insulins; Part 15 Public Hearing (May 13, 2019)
	Draft guidance providing clarity to biosimilar applicants who seek approval for fewer than all conditions of use for which a reference product is licensed
	Develop an enhanced version of the Purple Book for biological products
	Evaluate FDA's regulations regarding the submission and review of BLAs to ensure that they account for current practices and authorities
	Reference Product Exclusivity for Biological Products Filed Under Section 351(a) of the PHS Act; Final Guidance
Goal 3	New communication materials to educate providers and patients about biosimilars

BPCI Act Transition on March 23, 2020

- Section 7002(e)(4)of the BPCI Act provides:

  An approved application for a biological product under section 505 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355) shall be deemed to be a license for the biological product under such section 351 [of the PHS Act] on the date that is 10 years after the date of enactment of [the BPCI Act]

- FDA guidance announced that approved NDAs for "deemed products" will be **transitioned to 351(a) BLAs**.
- Applicants can seek licensure of products that are biosimilar to, or interchangeable with, transitioned products via 351(k).
  - FDA intends to issue additional guidance on this subject.

BPCI Act Transition on March 23, 2020

- In December 2018, FDA issued updated guidances on the statutory transition explaining FDA policy and thinking on *deemed BLAs.*
- FDA is working with applicants to minimize the effect of the transition, including through development-stage (BsUFA) meetings.
- We think FDA's performance goal dates, timelines for review, and recommendations to sponsors have made it unlikely that any proposed or pending applications submitted under the FD&C Act would be affected
- The Agency intends to maintain goal dates for completion of review of pending supplements.

BPCI Act Transition on March 23, 2020

- Differences between NDA and BLA regulations may result in some minor differences in labeling and CMC requirements
  - We expect the practical effects to be minimal
- Examples of differences include areas in carton and container labeling, required content of prescribing information.
- FDA has announced its intent to adopt a compliance policy for the labeling of biological products that are the subject of deemed BLAs.
  - This should minimize disruption and burden associated with differences between NDA and BLA labeling.
  - FDA does not intend to enforce BLA labeling requirements for transition products until March 23, 2025.

BPCI Act Transition on March 23, 2020

- Part 15 Hearing—May 13, 2019: The Future of Insulin Biosimilars: Increasing Access and Facilitating the Efficient Development of Biosimilar and Interchangeable Insulin Products. FDA seeking input on:
  - Biosimilar and interchangeability development requirements for insulins
  - Use with insulin pumps, over-the-counter insulins
  - Aspects of patient experience important in evaluating proposed biosimilar and interchangeable insulins

Biologics Regulatory Modernization

- The BLA regulations were written before addition of the 351(k) pathway.
- We are working to update and modernize the Agency's biological product regulations with targeted revisions related to the submission and review of BLAs.
- Updated regulations will provide enhanced clarity and regulatory certainty to manufacturers of both originator and biosimilar/interchangeable products, and will help prevent "gaming" that could prevent or delay competition.

Purple Book

- **FDA's Purple Book** provides a list of biological products licensed under the PHS Act, includes:
  - Information about biosimilarity, interchangeability
  - Information about exclusivity
- **An enhanced Purple Book is in development:**
  - Improved interface to provide user-friendly information to the public about approved biologics
  - Enhanced information for patients, prescribers, pharmacists, and other stakeholders

Education

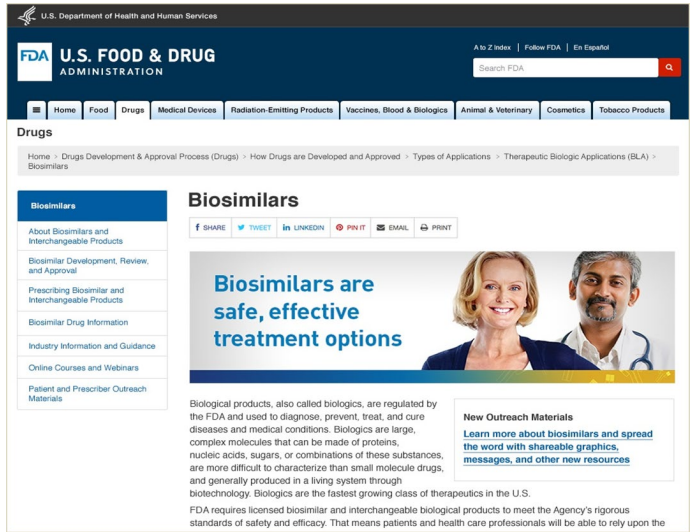
FDA is committed to developing effective communications to improve understanding of biosimilars among patients, health care providers, and payors.

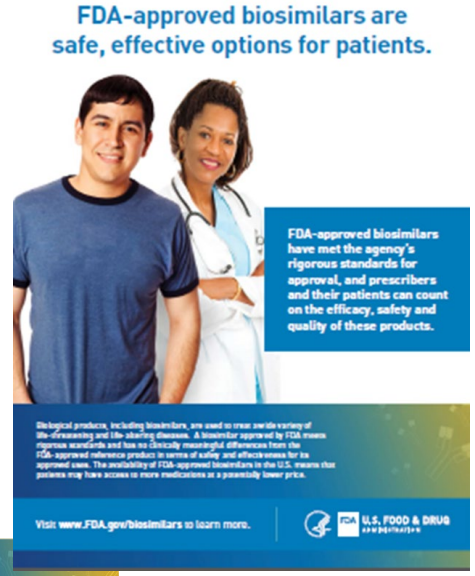
- October 2017: Initial Campaign Launch: prescriber outreach materials to help promote understanding of biosimilars and interchangeable products, including graphics, drop-in content, and social media messages.
- Webinars to educate HCPs in December 2017 and 2018
- Released a 5-part video series in May 2018

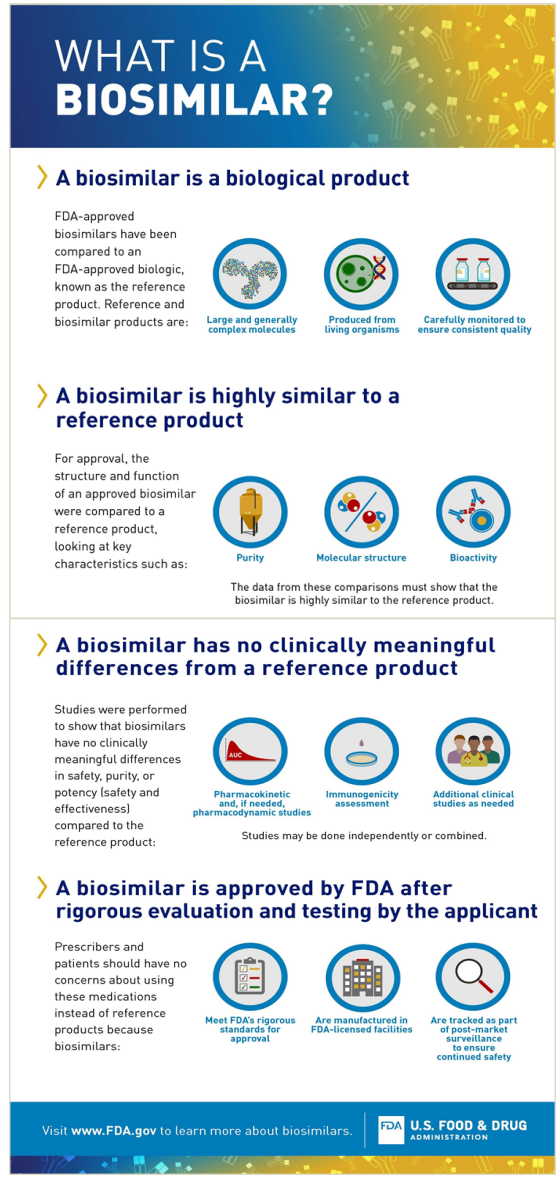
Stakeholder Outreach and Involvement

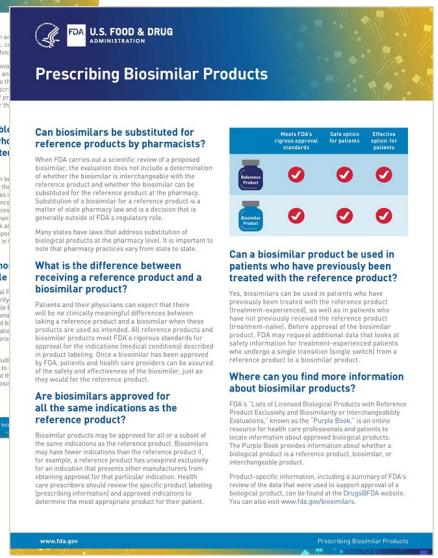
- Stakeholders play a key role in reaching the target audience
- As part of the campaign, FDA provided materials and talking points to facilitate dissemination of content to their audiences through channels unique to each stakeholder
- FDA has robust stakeholder engagement each month to continue momentum and interest in the campaign: For example, participated in Reddit AMA & Susan G. Komen Webinar, in addition to other efforts

Education Materials









Postmarket Safety Program

Sentinel Recompete

- Two year planning for new contract solicitation
  - Issued RFI
  - Two public meetings
  - Met with 18 potential vendors
- Request for proposal March 25; due May 24
- New vision for Sentinel and RWE

Envisioned New Sentinel: Three (or more) Centers

- Operations Center (largest Center)
  - Coordinate data partner network, infrastructure management and data curation
  - Conduct regulatory analysis
  - Host FDA Catalyst: RWE generation test bed
- Innovation Center(s)
  - Coordinating Center for methods development, data science and advanced analytics
- Community Building and Outreach Center
  - Coordination Center for community development, convening, hosting and knowledge management

Drug Compounding Program

Policy development

Stakeholder engagement

Risk-based oversight

Policies Issued in Late 2018 and Early 2019

- Revised draft guidance concerning good manufacturing practice requirements for outsourcing facilities (December 2018)
- Final rule concerning amendments to the regulation regarding the list of drug products that have been withdrawn or removed from the market for reasons of safety or effectiveness (December 2018)
- Final rule concerning the list of bulk drug substances that can be used to compound drug products under Section 503A (February 2019)
- Final guidance on evaluation of bulk drug substances nominated for use in compounding under section 503B (March 2019)
- Federal register notice concerning two bulk drug substances that FDA has determined not to include on the 503B bulks list (March 2019)

2019 Compounding Policy Priorities Plan

- Proposed federal register notice concerning bulk drug substances that FDA is proposing to include or not include on the list of bulk drug substances under section 503B for which there is a clinical need
- Proposed rule concerning the list of bulk drug substances that can be used to compound drug products under Section 503A
- Revised draft guidance on hospital and health system compounding
- Final memorandum of understanding between a state and the FDA addressing certain distributions of compounded human drug products
- Final guidance concerning insanitary conditions at compounding facilities

2019 Stakeholder Engagement

- FDA will be holding a public meeting in May 2019 to hear stakeholder perspectives concerning access to office stock from outsourcing facilities in light of FDA's enforcement policies as proposed in the revised draft guidance on current good manufacturing practice
- FDA meets with stakeholder organizations including pharmacy, medical, hospital, insurer, and industry organizations, as well as consumer groups and outsourcing facilities, to hear their views on matters related to compounding. FDA has held six sets of listening sessions with more than 75 stakeholders, and will be holding these listening sessions again in June 2019
- FDA hosts intergovernmental working meetings with representatives of the state boards of pharmacy to increase and improve our collaborative efforts to oversee compounding throughout the United States. FDA will be holding its eighth such meeting in October 2019

Building New Engagement Programs

- In 2019, FDA will utilize appropriated funds provided in FDA's 2019 budget to lay the groundwork for the "Center of Excellence on Compounding for Outsourcing Facilities," including training on current good manufacturing practice requirements for outsourcing facilities
- More updates and opportunities for public participation in this effort will be forthcoming

FDA Oversight Priorities

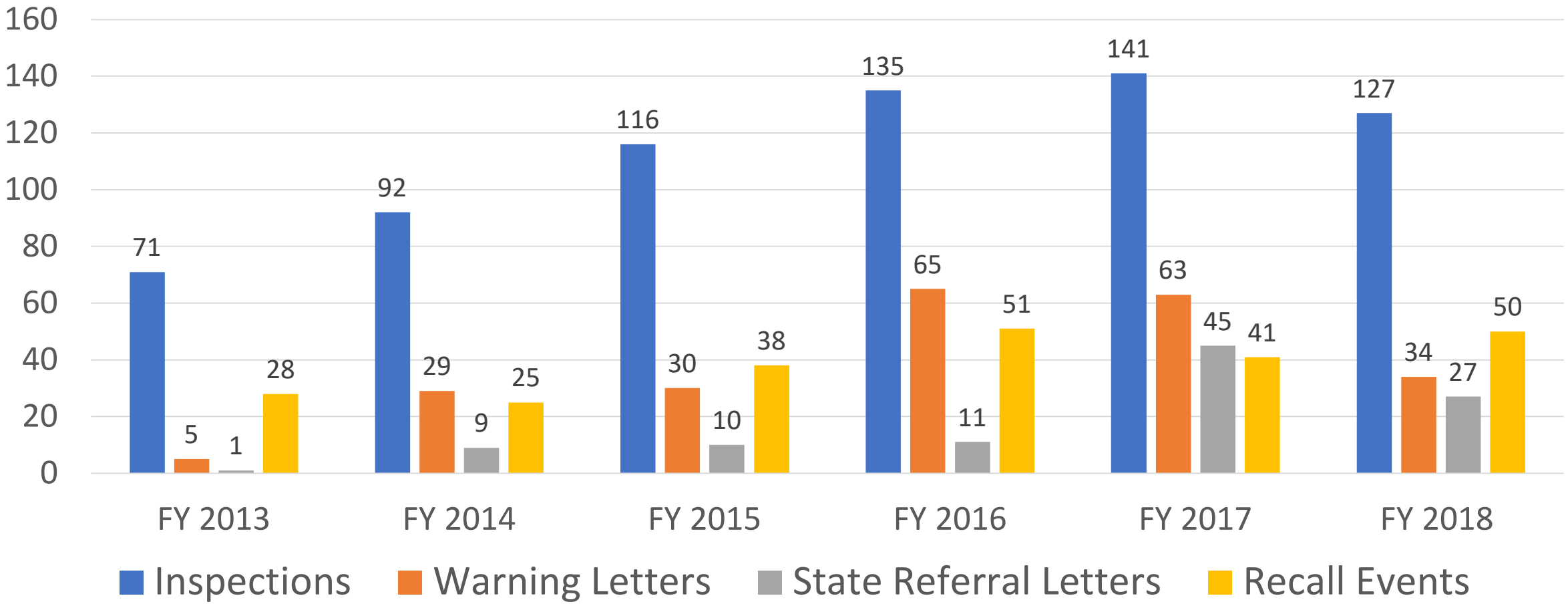
- Focus oversight on entities whose practices may have the greatest impact on public health
  - Conduct oversight of the outsourcing facility sector to evaluate compliance with the law, encourage voluntary compliance, and pursue regulatory action when necessary
  - Conduct risk-based oversight of entities that are not outsourcing facilities, but that engage in multi-state, large volume distribution of compounded drugs. These compounders' interstate operations may present challenges for state regulators, and their practices may have widespread, nationwide impact
  - In general, FDA does not intend to engage in routine surveillance of state-licensed pharmacies that operate within their state

Compliance and Regulatory Actions

Since enactment of DQSA

- Approximately 700 inspections of compounders, and more than 180 of these inspections were for-cause
- More than 220 Warning Letters issued
- More than 230 Recall Events
- 10 injunctions of compounders
- Worked with the Department of Justice on several criminal actions involving compounders

Compounding Oversight and Inspections



Opioid Regulation

Role of Citizen Petitions in FDA's Regulation of Opioids

Citizen Petitions can play an important role in helping FDA develop and articulate opioids policy. FDA has responded to some petitions requesting action on opioids; several remain pending. Some raise important issues that require a broader public discussion. Some touch on statutory authority.

- **Safety Labeling Changes/PMRs:** In 2013 FDA made important safety labeling changes to ER/LA opioid analgesics and required new post-market studies and trials to assess risks of misuse & abuse associated with ER/LA opioids, partially in response to a 2012 citizen petition.
- **Naloxone Co-prescribing:** In 2018 FDA held an advisory committee on the merits of co-prescribing naloxone with opioid analgesics, an issue raised in a 2016 citizen petition.
- **Abuse-deterrent formulations:** FDA has received many citizen petitions requesting additional action on abuse-deterrent opioid formulations. We granted one of these requests when we determined that original OxyContin was withdrawn for safety reasons in 2013; we have denied several others.
- **Higher doses:** A pending citizen petition asks FDA to remove what it characterizes as "ultra high dosage unit" opioid analgesics from the market, defining this group as those that exceed 90 MME/day when taken as directed in labeling. FDA just announced a June 11-12 advisory committee on safety concerns and clinical utility associated with the higher range of opioid analgesic dosing.

Substance Use-Disorder Prevention that Promotes Opioid Recovery and Treatment (SUPPORT) for Patients and Communities Act

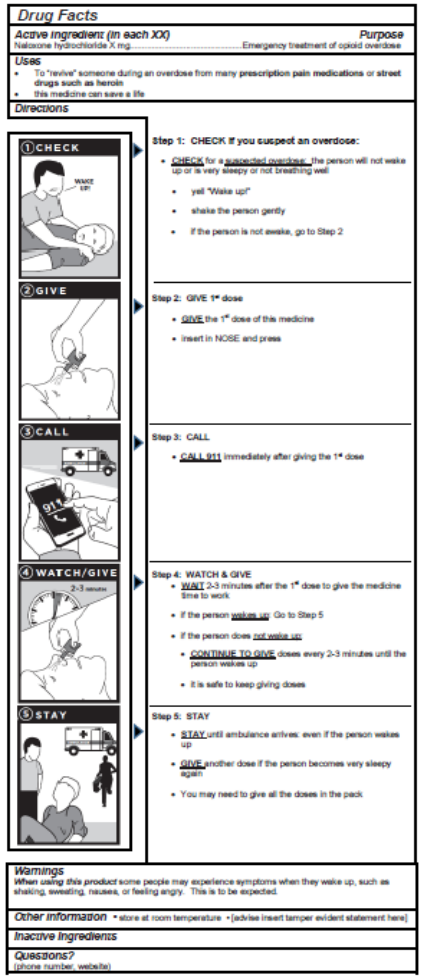
Many new provisions affect FDA. Implementation is ongoing.

- **New Packaging/Disposal Mandate** – new REMS authority to require safety-enhancing packaging/disposal for drugs with serious risk of abuse or overdose
- **Expanded PMR & Labeling Change Authority** – change to definition of "adverse drug experience" intended to clarify FDA's authority to require long-term efficacy studies of opioids; expanded authority to modify drug labeling
- **Expanded Import Control –** new authority to treat certain articles as drugs if they contain APIs for the purposes of determining admissibility at IMFs, without having to first determine intended use
- **Expanded Debarment Authority –** new authority to debar based on felony conviction related to drug imports and to treat drugs imported by debarred person adulterated or misbranded
- **Stop distribution/Recall of Controlled Substances** – new authority to stop distribution and recall controlled substances that pose reasonable probability of serious adverse health consequences or death
- **Opioid Prescribing Guidelines Mandate** – FDA must develop evidence-based guidelines for indication-specific treatment of acute pain where such guidelines do not exist
- **Non-addictive Pain Treatments/MAT Guidance Mandate –** FDA must hold public meeting and produce guidance(s) to address the challenges and barriers of developing non-addictive medical products intended to treat acute or chronic pain or addiction

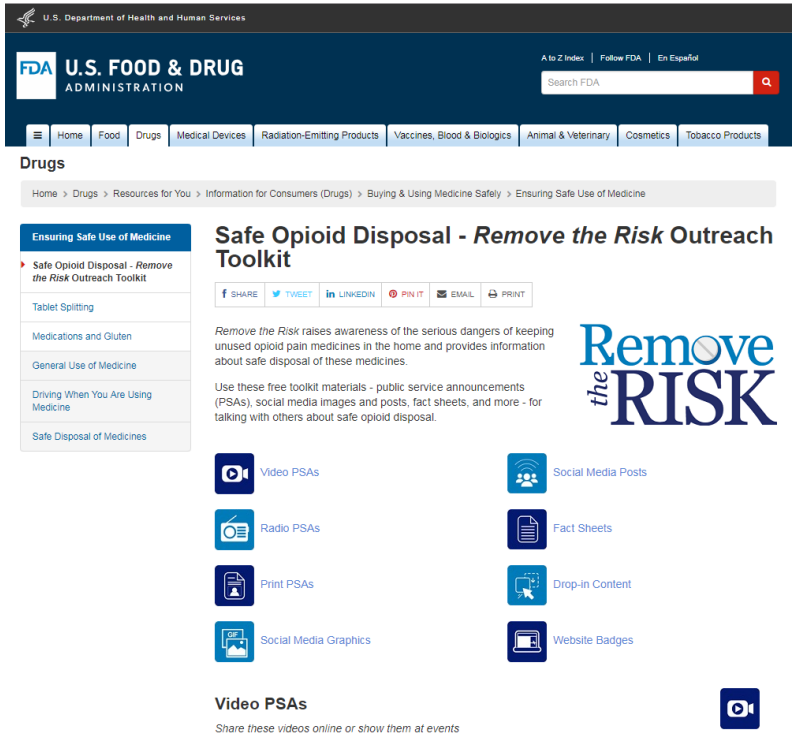
Community Involvement: OTC Naloxone and Safe Opioid Disposal

On January 17, 2019 FDA announced the availability of two model Drug Facts Labels (DFLs) containing information a consumer needs to administer naloxone safely and effectively.

FDA proactively designed, tested and validated the key labeling requirements necessary to approve an OTC version of naloxone and make it available to patients.



On April 25, 2019 FDA launched public education campaign to encourage safe removal of unused opioid pain medicines from homes.



Summary

- As usual, CDER has a lot on its plate
- Driven by Congressional mandates, rise in regulatory workload and user fee agreements
- Other important initiatives not covered here include
  - Workflow management and other IT platforms
  - Further submission standardization
  - Advanced pharmaceutical manufacturing
- CDER is focusing on informatics and governance to help manage these multiple time-sensitive programs

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