State of Biosimilars and Generics 2024

AAM GRx + Biosims CDER Keynote
October 23, 2024

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U.S. FOOD & DRUG ADMINISTRATION

Disclosures

- No financial disclosures

- This presentation reflects the views of the author and should not be construed to represent FDA's views or policies.

Areas We Will Cover Today

- FY24 Highlights (approvals, guidances, etc.)
  - GDUFA
  - BsUFA
- Collaboration/Engagement Efforts (global, industry meetings, education/outreach efforts)
- Product Quality
- Compliance
- Final thoughts

FY24 HIGHLIGHTS – GENERIC DRUG PROGRAM

Recognizing Forty Years of the Hatch-Waxman Amendments

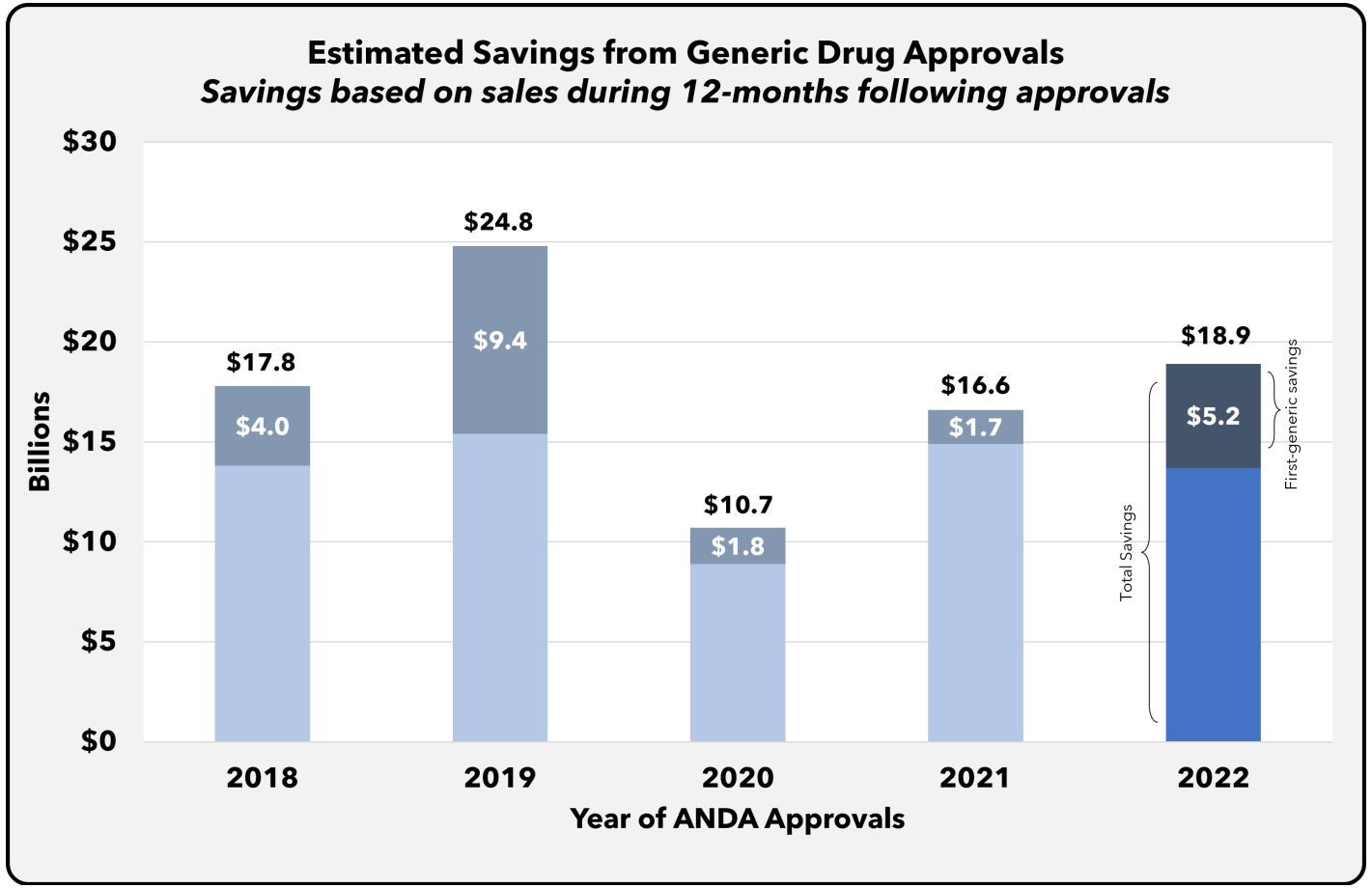
Highlighted FY24 Generic Drug Program Metrics

- more than 850 ANDAs approved or tentatively approved, including:
  - 70 First Generics
  - 88 complex generics
- 77 pre-ANDA meeting requests for advice on the development of complex generic products
- More than 200 new and revised product-specific guidances (PSGs) describing FDA's current thinking and expectations, including:
  - 31 PSGs that provided a more efficient bioequivalence approach
  - 20 PSGs for complex drug products

FY2024 First Generic Examples

Generic Name	Brand Name	Indication	Approval Date
Pazopanib Tablets	Votrient	Advanced renal cell carcinoma; advanced soft tissue sarcoma	October 2023
Teriparatide Injection	Forteo	Osteoporosis	November 2023
Fidaxomicin Tablets	Dificid	C. difficile-associated diarrhea	January 2024
Dronedarone Tablets	Multaq	Atrial fibrillation	January 2024
Deflazacort Oral Suspension	Emflaza	Duchenne muscular dystrophy	April 2024
Edaravone Injection	Radicava	Amyotrophic lateral sclerosis (ALS)	May 2024
Emtricitabine and Tenofovir Alafenamide Tablets	Descovy	HIV-1 infection	May 2024

Advancing Public Health by Improving Access to Medication

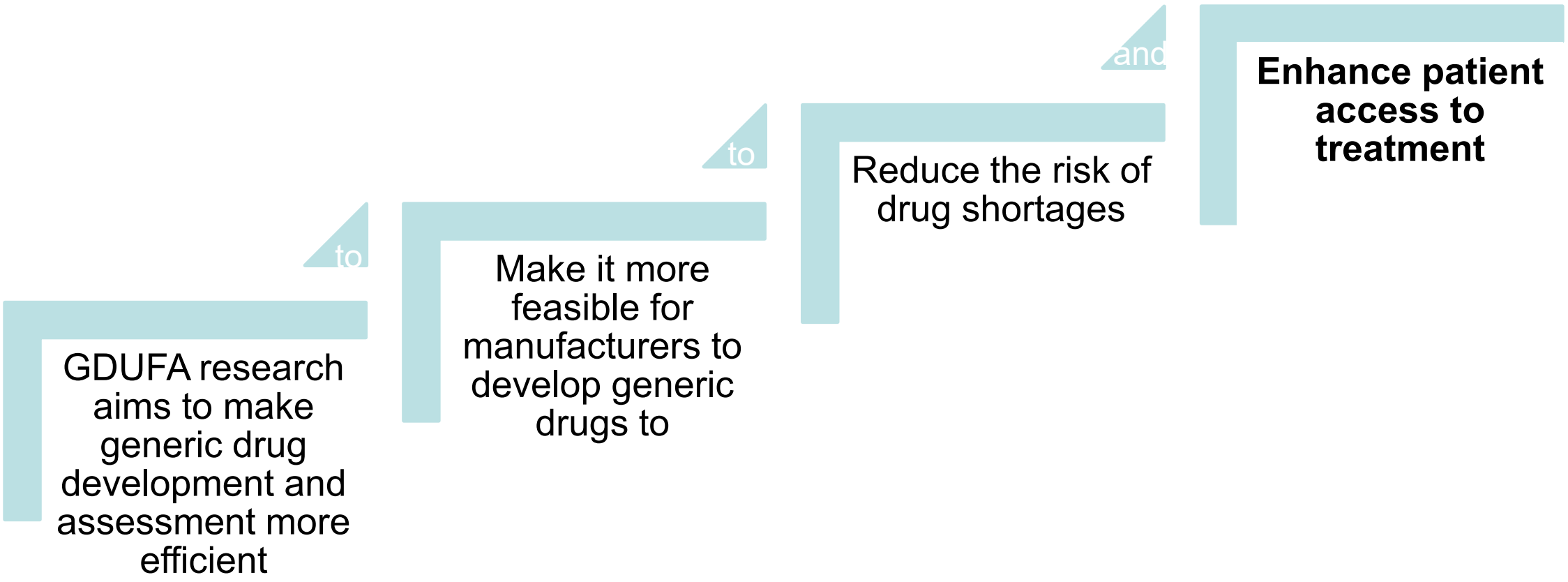


Suitability Petitions

FDA will review and respond to suitability petitions that have been assigned a goal date as follows, within 6 months after completeness assessment:

- FDA has received over 100 Suitability Petitions in FY 2024.
- 95% of Suitability Petitions were completed within 6 months after the FDA completeness assessment.

GDUFA Science and Research Improves Patient Access



Model-Integrated Evidence Pilot (MIE)

Address innovative generic drug development challenges that cannot be sufficiently addressed by existing pre-ANDA and ANDA scientific meetings

Focus on discussing scientific and technical topics of using model-integrated evidence strategies for establishing bioequivalence

Webinar - A Deep Dive: FDA's Model-Integrated Evidence Industry Meeting Pilot Program for Generic Drugs

International Collaboration

M13A Bioequivalence for Immediate-Release Solid Oral Dosage Forms

- Final M13A guidance: **harmonized, global, scientific recommendations** for conducting BE studies during both development and post approval phases that can increase the efficiency of drug development and accelerate the availability of safe and effective orally administered IR solid oral dosage forms.

- M13 is the first ICH guidance developed on harmonizing BE standards for generic drugs following the publication of the ICH Reflection Paper "Further Opportunities for Harmonisation of Standards for Generic Drugs" (November 2018).

FDA webinar

An Invitation: Generic Parallel Scientific Advice

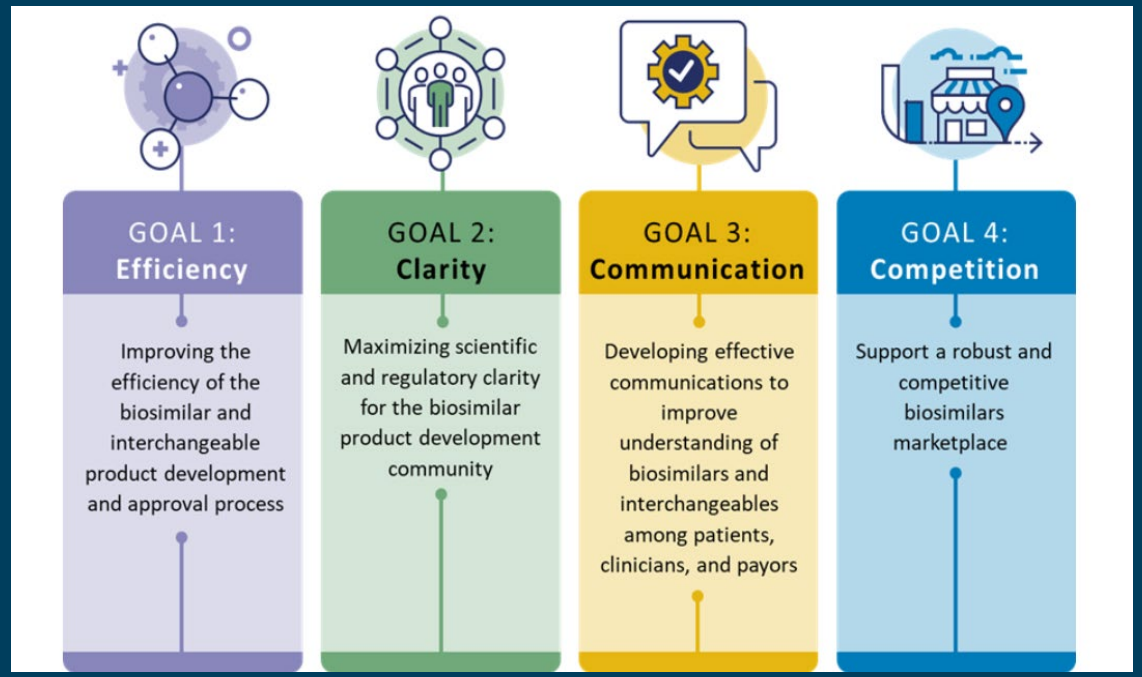
What: A voluntary pilot program to facilitate discussions between generic drug developers, FDA, and the European Medicines Agency

Why: Prospective generic drug applicants can engage in concurrent scientific conversation with both agencies on key issues

How: Request a meeting to address specific scientific inquiries around the development of complex generic drug products by emailing a "Request for Parallel Scientific Advice" justification to

EMAinternational@EMA.Europa.EU **and** preANDAhelp@FDA.HHS.gov

FY24 HIGHLIGHTS – BIOSIMILAR PROGRAM



UPDATES & MILESTONES

FDA approved the 50th biosimilar!

- This year, we also saw several biosimilar approvals to new reference products, including denosumab, eculizumab, and aflibercept

Updated Biosimilars Action Plan

- Web-based format with deliverables that that will promote biosimilar development, communication, clarity, and adoption.

Released 2018 BAP Summary Report

- Describes progress and goals achieved since 2018

FDA Approved Biosimilar & Interchangeable Biosimilars

61 Approved Biosimilars

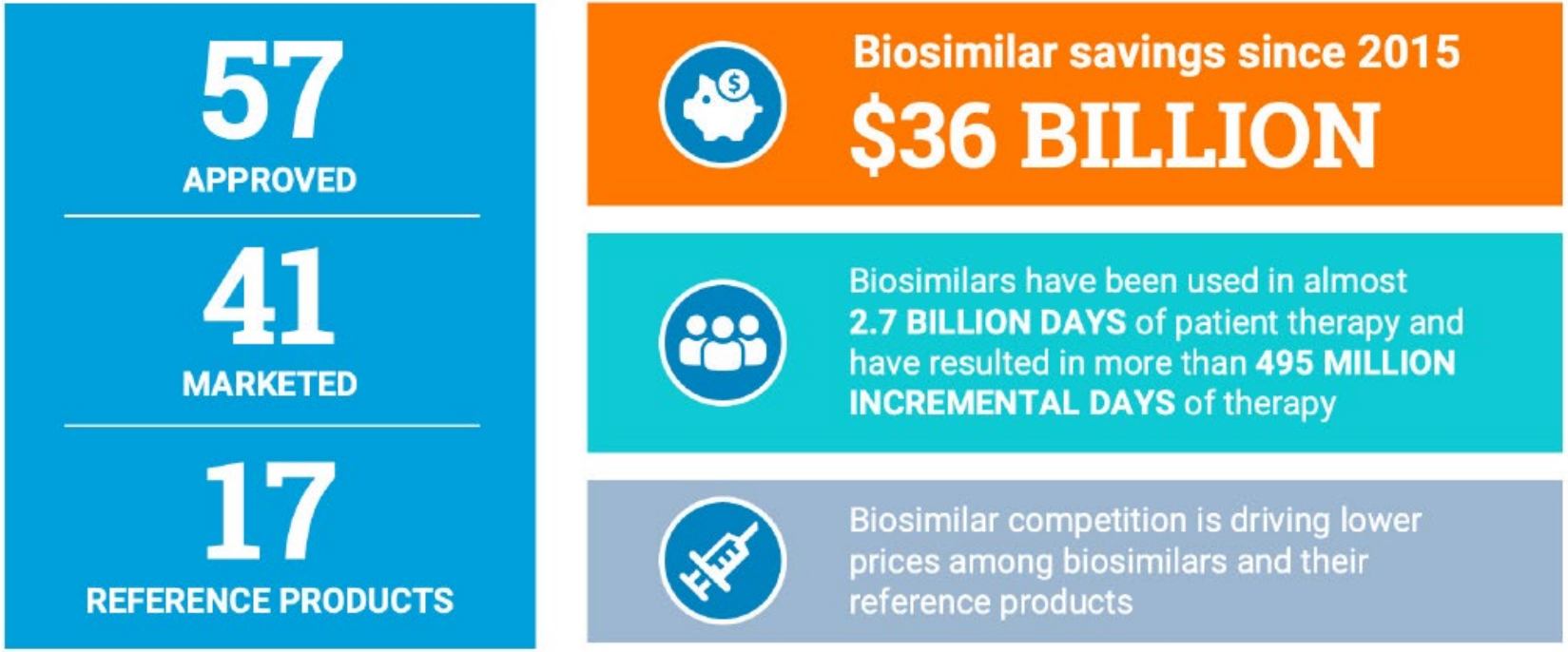
17 Reference Products

41 Marketed

Filgrastim 4	Trastuzumab 6	Natalizumab 1	Aflibercept 5
Epoetin 1	Infliximab 4	Ranibizumab 2	Eculizumab 2
Pegfilgrastim 6	Etanercept 2	Tocilizumab 2	
Rituximab 3	Adalimumab 10	Ustekinumab 5	
Bevacizumab 5	Insulin Glargine 2	Denosumab 1	

As of Sept 28, 2024

Biosimilars Market Overview



SOURCE: AAM / THE U.S. GENERIC & BIOSIMILAR MEDICINES SAVINGS REPORT September 2024

BsUFA Meeting Management

- Modifies the BIA meeting so preliminary comparative analytical data is no longer required to meet with FDA.
  - As of 9/11/24: ~17 meetings, compared to 11 in FY23

- Introduces a new Biosimilar Product Development meeting type: Type 2a, focused on a narrow set of issues.
  - As of 9/11/24: Type 2a = 35; Type 2b = 51 (total 86) compared to Type 2a = 40; Type 2b = 46 in FY23

**Note: This is preliminary data and will change depending on the cohort*

BsUFA Regulatory Science Program Updates

Released Revised Roadmap in January 2024

- Provides updated information about the research priorities based on stakeholder feedback.

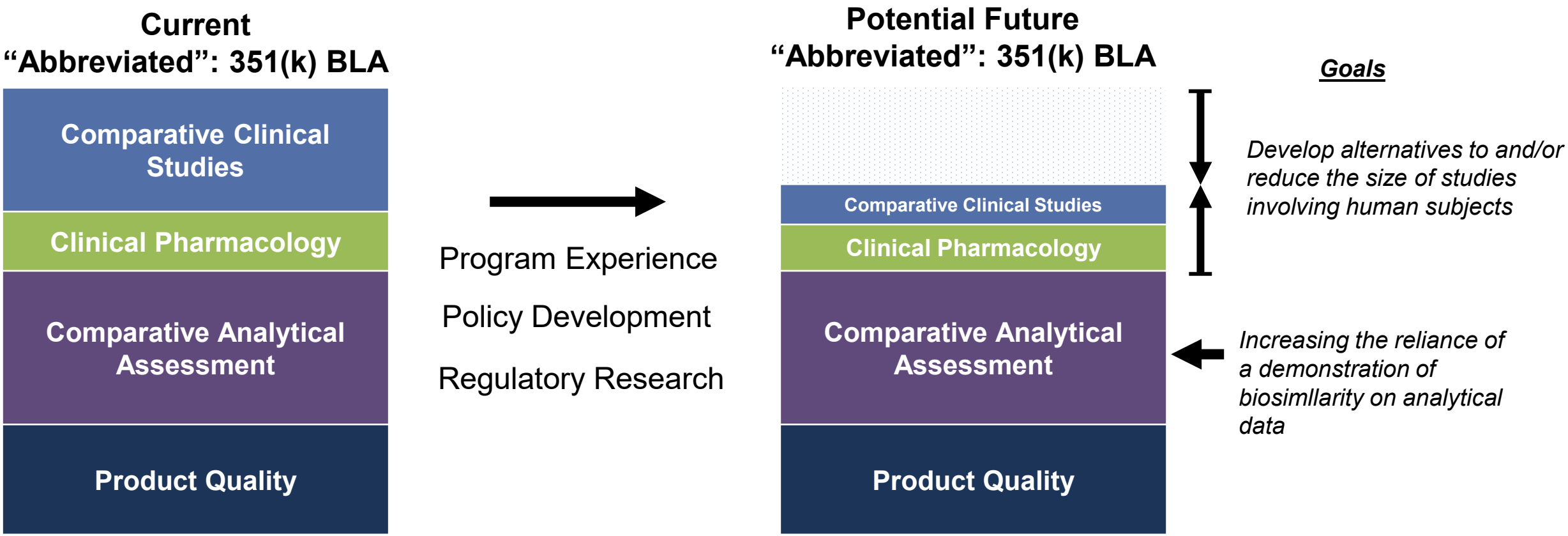
- Revised priorities are focused into two areas related to the data package to support approval of a biosimilar or interchangeable biosimilar:

    1. Increasing the reliance on analytical data in a demonstration of biosimilarity
    2. Developing alternatives to and/or reduce the size of studies involving human participants

All materials can be found at: https://www.fda.gov/drugs/biosimilars/biosimilars-science-and-research

*Including videos and summary of Oct 2023 stakeholder engagements and a summary of the entire BsUFA Reg Sci Portfolio as of Dec 2023

Regulatory Science Pilot Program Goals Focus on Composition of the 351(k) Data Package



BsUFA Regulatory Science Program: What's Next?

Ongoing Stakeholder engagement:

- Biosimilar Roundtables with Reagan-Udall
  - Series of 6 roundtables with biosimilar developers
  - Focused on developers with limited FDA engagement experience
  - Summary report will be available after roundtables conclude

Upcoming:

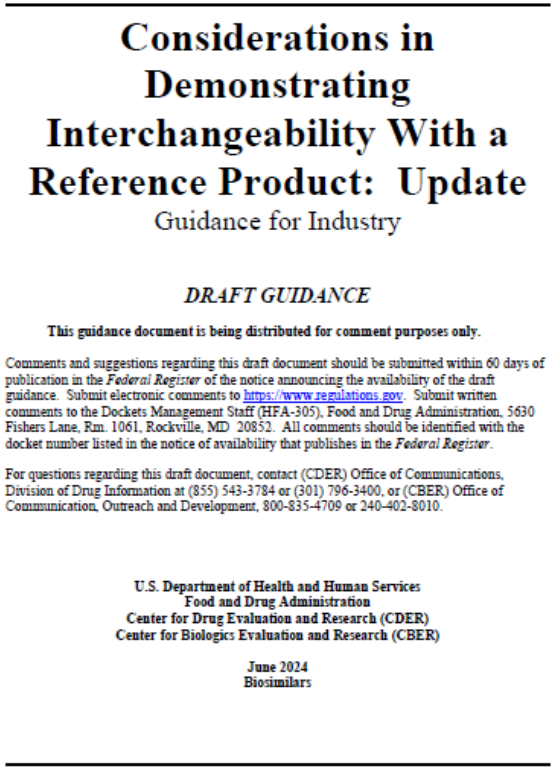
- 2024 Annual Reports for entire research portfolio posted publicly fall/winter 2024
- New FY25 BAA Funding Opportunity
- SBIA Public Webinar with updates on program planned for January 2025

Recent BsUFA Guidance Updates

- **Guidance for use-related risk analyses (9/30/2024)**
  - **Released 7/08/24**
- **Guidance for promotional labeling and advertising (9/30/2024)**
  - Revised 2020 draft- **Released 4/24/24**
- **Guidance on postapproval manufacturing changes (9/30/2024)**
  - **Released 7/23/24**
- **Guidance for device/presentations/CC for interchangeables (9/30/2025)**
  - In Progress

2024 Interchangeability Draft Guidance Update

- FDA has generally recommended switching studies in the past as part of the data package needed to demonstrate interchangeability of a biosimilar; however, of the 15 approved interchangeable biosimilars, 13 were approved without additional clinical (switching study) data.
- Experience has shown that for the products approved as biosimilars to date, the risk in terms of safety or diminished efficacy is insignificant following single or multiple switches between a reference product and a biosimilar product.
- This draft guidance:
  - Outlines a revised approach where switching studies will generally not be needed
  - Provides clarity and transparency about the FDA's thinking
  - Aligns the review and approval process with existing and emerging science
- Both biosimilars and interchangeable biosimilars meet the same high standard of biosimilarity for FDA approval and both are as safe and effective as the reference product.



Considerations in Demonstrating Interchangeability With a Reference Product: Update

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 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 (CDER) Office of Communications, Division of Drug Information at (855) 543-3784 or (301) 796-3400, or (CBER) Office of Communication, Outreach and Development, 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)

June 2024
Biosimilars

VIEWPOINT

The Science of Biosimilars—Updating Interchangeability

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Published Online: September 18, 2024. doi:10.1001/jama.2024.15225

Before discussing how our thinking has evolved, we need to clarify an important point. The interchangeability standard does not mean that a biosimilar cannot be used in place of the reference product unless it has an interchangeability designation. To the contrary, a health care professional can prescribe a biosimilar for any patient in place of the reference product. This means that FDA's biosimilarity assessment must address any potential risk faced by a patient using a biosimilar product in place of the reference product, including the risk of an adverse immune reaction, whether treatment-naive or previously treated with the reference product. By now, significant evidence from these assessments has shown that for the biosimilars approved to date, the risk in terms of safety or diminished efficacy is insignificant following single ormultiple switches between a reference product and a biosimilar product.[4]

4. Herndon TM, Ausin C, Brahme NN, et al. Safety outcomes when switching between biosimilars and reference biologics: a systematic review and meta-analysis. PLoS One. 2023;18(10):e0292231. doi:10.1371/journal.pone.0292231

Additional Biosimilar Updates

FDA's 2025 Fiscal Year Legislative Proposal includes:

- Elimination of the Statutory Distinction Between the Approval Standard for Biosimilar and Interchangeable Biosimilar Products and Deem that Approved Biosimilars are Interchangeable
  - Confusion/misunderstanding among patients and health care providers about S&E of biosimilars and whether they are less S&E than interchangeable biosimilars
  - U.S. biosimilar program more consistent with current scientific understanding, global regulatory approach, incl. E.U.
  - Potential to increase uptake of biosimilars, competition, access, affordability

Center for Medicare & Medicaid Services Revises Policy for Biosimilars:

- More Flexibility to More Quickly Substitute Lower Cost Biosimilar Biological Products for Their Reference Products
  - For senior citizens, biosimilars may be substituted as formulary maintenance changes without prior CMS approval (previously only for interchangeable biosimilars)

BIOSIMILAR EDUCATION AND OUTREACH

Medscape CE Courses

82,385
TOTAL LEARNERS

19,328
TOTAL MD LEARNERS

61,227
TOTAL OTHER HCP LEARNERS

37,479
TOTAL TEST TAKERS

MD REACH

19,328 MDs
engaged, including:

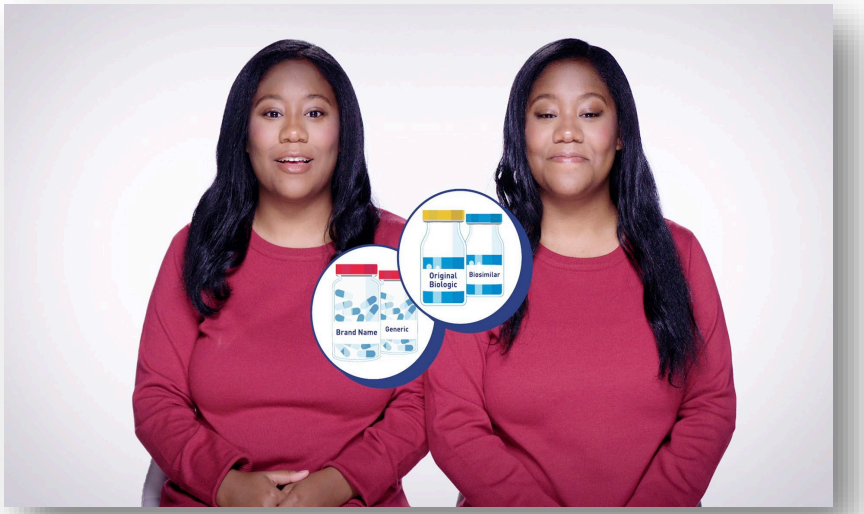
214	Neurologists
1,374	Ophthalmologists
2,317	Rheumatologists
2,199	Dermatologists
1,331	Gastroenterologists
161	Obstetricians & Gynecologists
7,789	Primary Care Physicians
3,943	Other Physicians

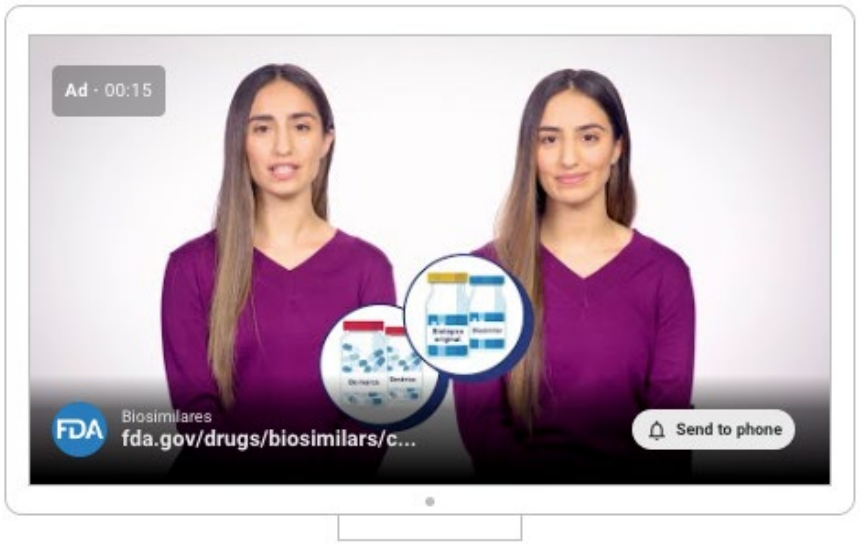
OTHER HCP REACH

61,227 Other HCPs
engaged, including:

5,023	Nurse Practitioners
722	Physician Assistants
35,230	Other Nurses
16,870	Pharmacists
3,382	Other HCPs

New Outreach and Education Activities





"Twins" PSA

- 30 and 15 Second PSAs in English and Spanish
- YouTube Ads Metrics above benchmark
- PSAs won a Gold Digital Health Award!

- 5.7M impressions
- 11.9K link clicks
- 0.22% average clickthrough rate
- 4.9 million video views
- 69.58% view rate
- 39% engagement rate

Updated Biosimilar Curriculum Toolkit

Updated biosimilar curriculum toolkit released October 16, 2024

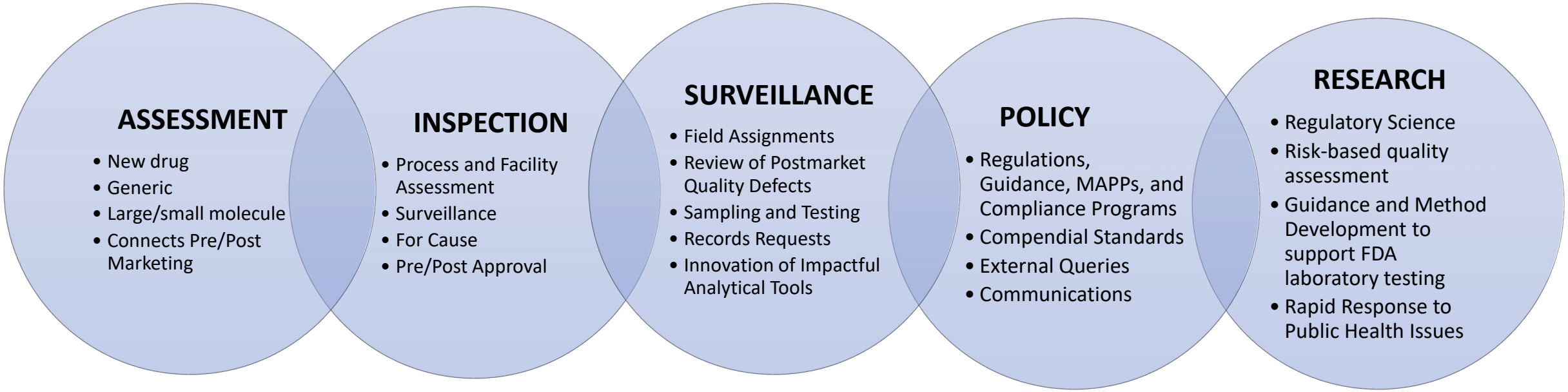
- Added additional topics to the existing curriculum:
  - Comparative Analytical Assessment
  - Quality Attributes
  - The Purple Book
  - Insulin and Interchangeability
  - Labeling
- New content includes 4 new videos, new case studies, information sheets, slides and discussion questions
- Updates based on stakeholder feedback

https://www.fda.gov/drugs/biosimilars/curriculum-materials-health-care-degree-programs-biosimilars

COMPLIANCE AND SUPPLY CHAIN

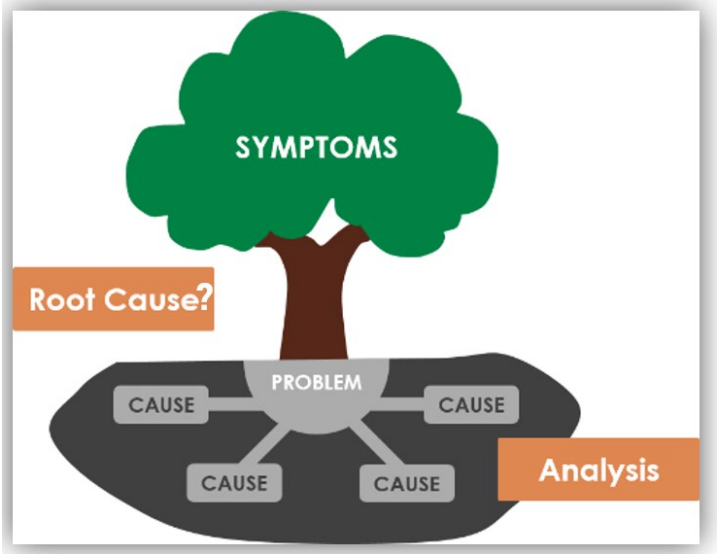
Ensuring Quality Across the Product Life Cycle

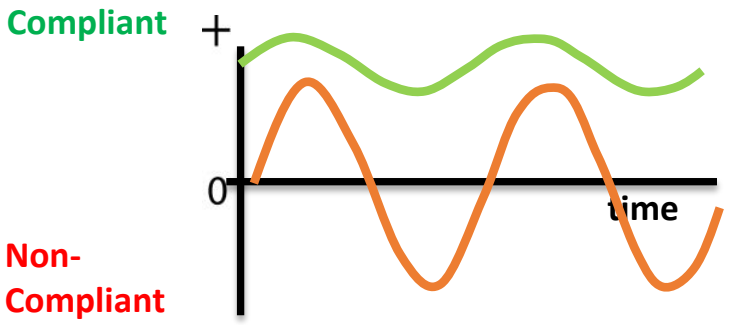
FDA's drug quality program is multimodal in nature



Culture of Sustained Quality

- Senior leaders are ultimately responsible for product quality
- CGMP contains a management oversight component
- Important to focus on lifecycle quality signals and root cause analysis





Company A: **Prevention-focused, results in consistent CGMP compliance.**

Company B: **Lapses in control due to reactive, inconsistent adherence to CGMP; vacillates between acceptable and substandard compliance**

Warning Letter Excerpt:
"Your firm's executive management remains responsible for resolving all deficiencies and systemic flaws to ensure ongoing CGMP compliance."

Achieving Sustainable Compliance

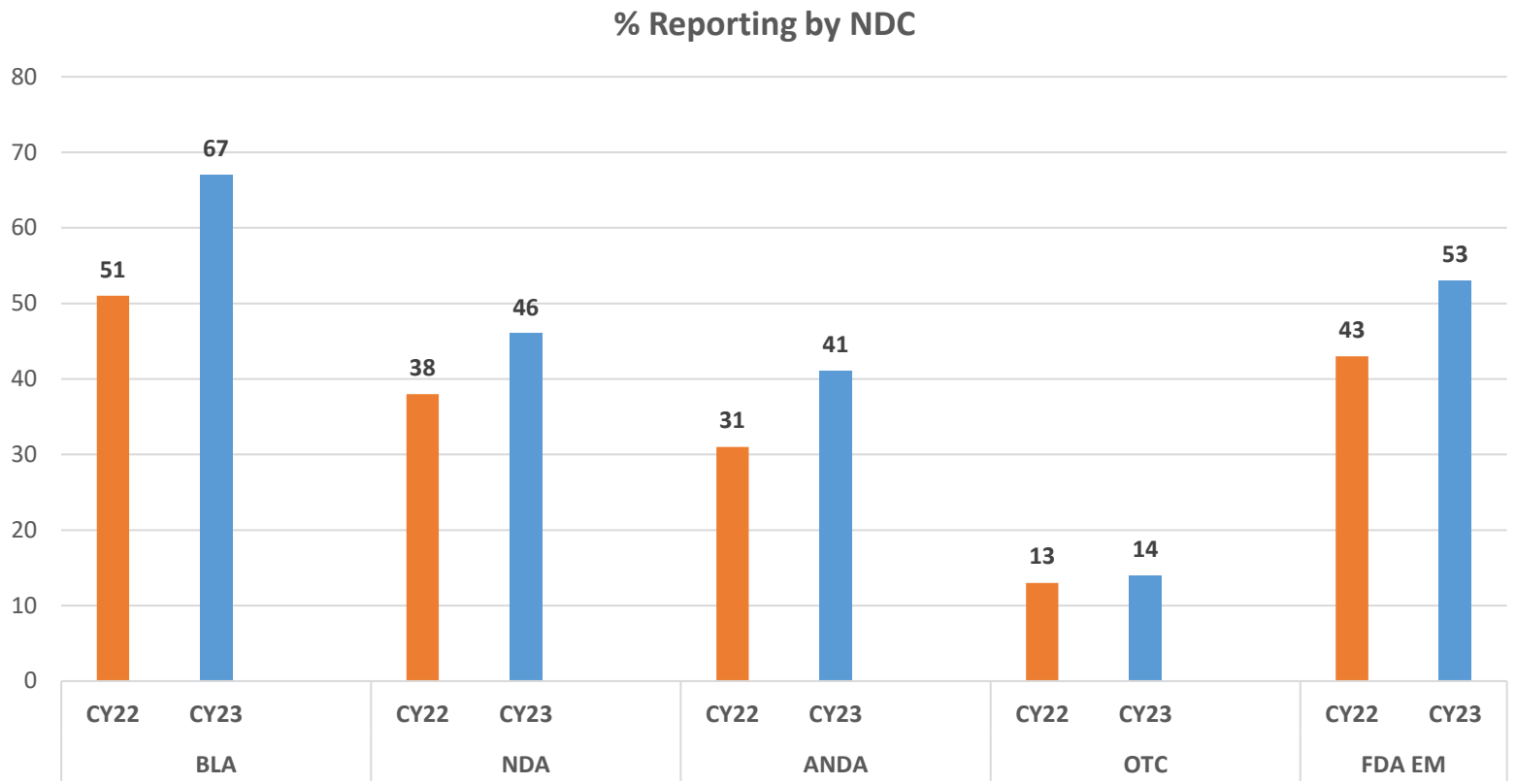
1. Implement long-term systemic remediation
2. Ensure strong quality management oversight
3. Foster a strong quality culture mindset
4. Ensure you have well-designed facilities, equipment, and processes
5. Engineer quality system to proactively identify and remediate problems as they occur

The Value of Drug Amount Reporting

- **FDA's vision for use of the CARES Act Drug Amount data:**
  - Combining drug amount reporting data with other information to enhance understanding of drug supply chain issues and drug shortages
  - Using the drug amount reporting data to evaluate an individual establishment's potential impact on drug supply chains
  - Strengthening CDER's risk-based Site Selection Model used for prioritizing surveillance inspections by better gauging potential patient exposure to a site's products

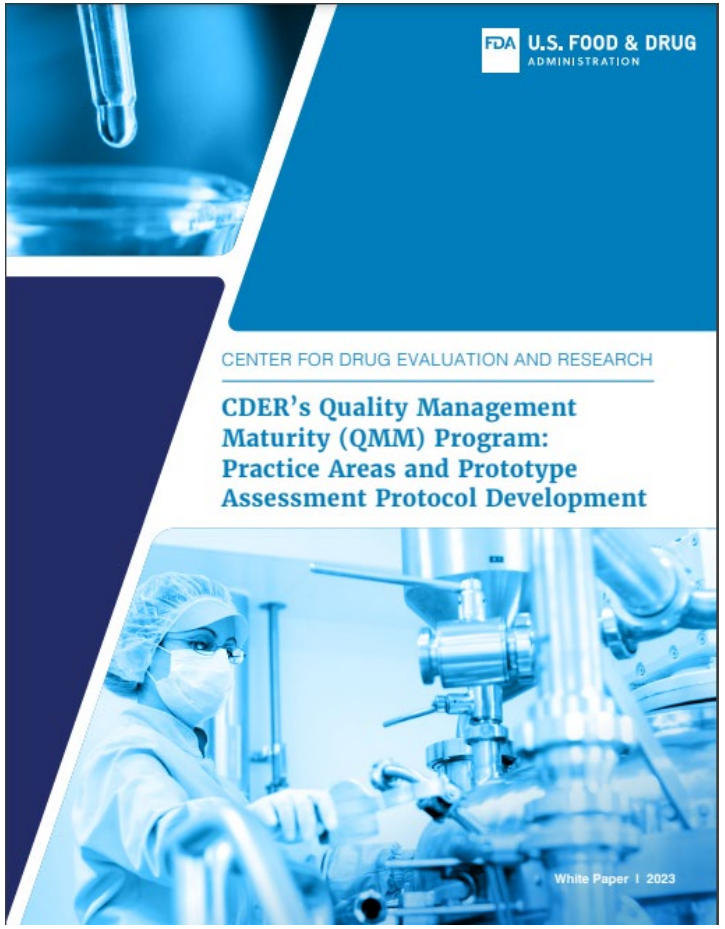
Drug Amount Submission Status – Summary Statistics

Table below shows the count of CDER regulated products reports submitted by product type for CY22 & CY23 as of 09/30/2024



Assessment of QMM

- CDER Program goals :
  - Foster a strong quality culture mindset
  - Minimize risks to product availability to ensure reliable market supply
- White paper describing five practice areas covered by a prototype assessment protocol published August 31, 2023
- Continuing stakeholder engagement; seeking feedback on elements of a QMM program
  - During September 15 – December 14, 2023, FDA solicited comments via an FRN and a public docket.
- Quality Management Maturity Prototype Assessment Protocol Evaluation Program



CDER Support for Advanced Manufacturing

ASSESSMENT AND INSPECTION

Emerging Technology Program (ETP)
&
Advanced Manufacturing Technologies (AMT) Designation Program

SCIENCE

Advanced Manufacturing Science & Research

POLICY

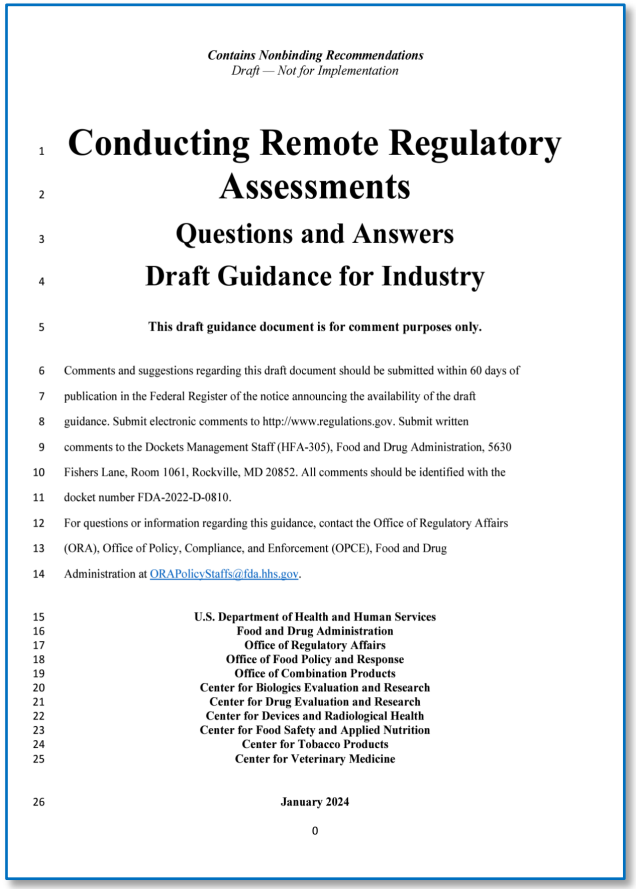
Framework for Regulatory Advanced Manufacturing Evaluation (FRAME)

COMPLIANCE & INSPECTIONAL WORK

Inspections

- In FY 2023, FDA-ORA conducted over 1000 human drug inspections (nearly a 30% increase over FY22) with over half being foreign facilities
- We also continue to use alternative tools like Remote Interactive Evaluations

Guidances Published



Contains Nonbinding Recommendations
Draft — Not for Implementation

Conducting Remote Regulatory Assessments

Questions and Answers

Draft Guidance for Industry

This draft guidance document is for comment purposes only.

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For questions or information regarding this guidance, contact the Office of Regulatory Affairs (ORA), Office of Policy, Compliance, and Enforcement (OPCE), Food and Drug Administration at ORAPolicyStaffs@fda.hhs.gov.

U.S. Department of Health and Human Services
Food and Drug Administration
Office of Regulatory Affairs
Office of Food Policy and Response
Office of Combination Products
Center for Biologics Evaluation and Research
Center for Drug Evaluation and Research
Center for Devices and Radiological Health
Center for Food Safety and Applied Nutrition
Center for Tobacco Products
Center for Veterinary Medicine

January 2024

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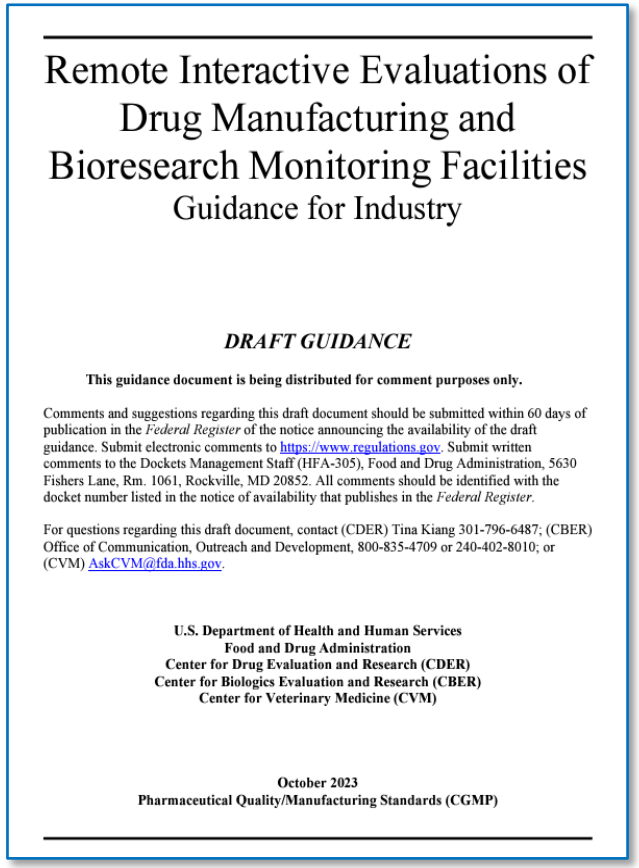

Remote Interactive Evaluations of Drug Manufacturing and Bioresearch Monitoring Facilities

Guidance for Industry

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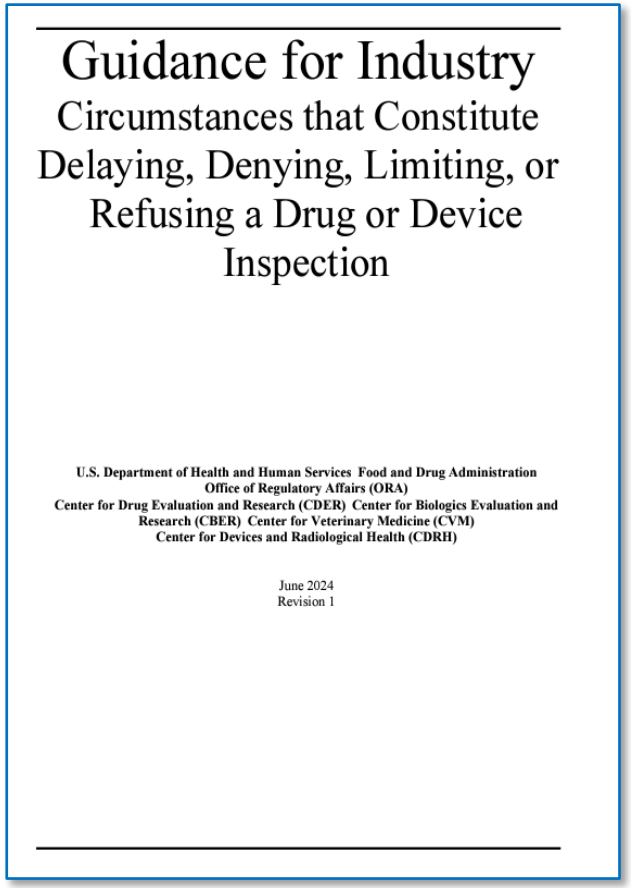
U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Veterinary Medicine (CVM)

October 2023
Pharmaceutical Quality/Manufacturing Standards (CGMP)



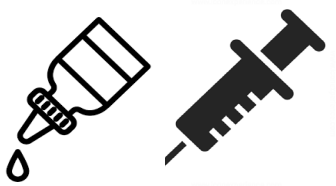
Guidance for Industry

Circumstances that Constitute Delaying, Denying, Limiting, or Refusing a Drug or Device Inspection

U.S. Department of Health and Human Services Food and Drug Administration
Office of Regulatory Affairs (ORA)
Center for Drug Evaluation and Research (CDER) Center for Biologics Evaluation and Research (CBER) Center for Veterinary Medicine (CVM)
Center for Devices and Radiological Health (CDRH)

June 2024
Revision 1

Recurring Compliance Issues in Drug Manufacturing



Sterility assurance and aseptic processing

Selection of ingredient suppliers and appropriate testing

Quality management related to contract manufacturing arrangements

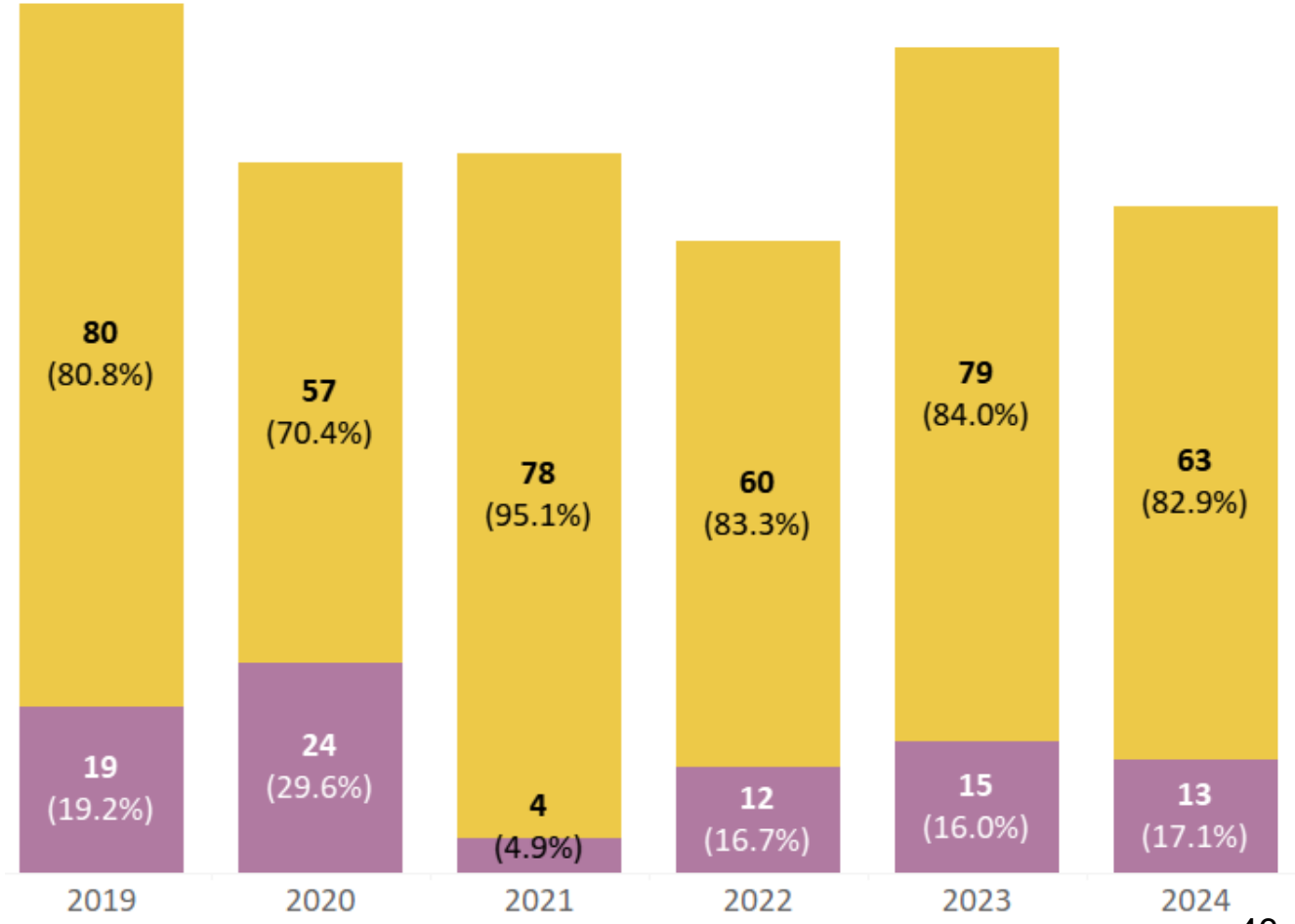
Data integrity, transparency, and record retention

Reference to Data Integrity in CGMP Warning Letters – FY20-24*

Does NOT Reference Data Integrity
References Data Integrity

Warning Letters Issued 10/1/2019 to 6/30/2024

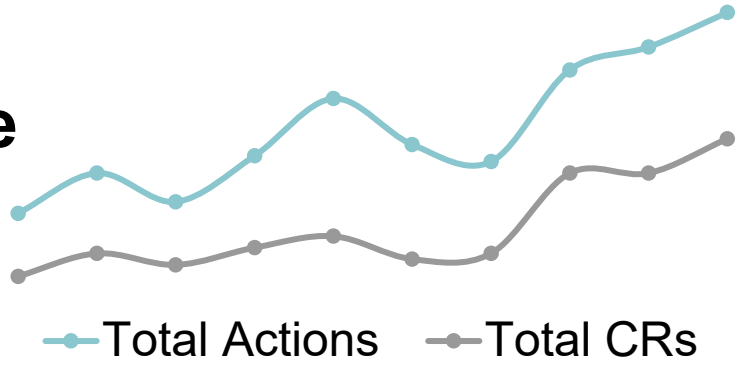
Non-Compounding CGMP Warning Letters



See Guidance for Industry: Data Integrity and Compliance with CGMP Guidance for Industry

Facts Related to BLAs

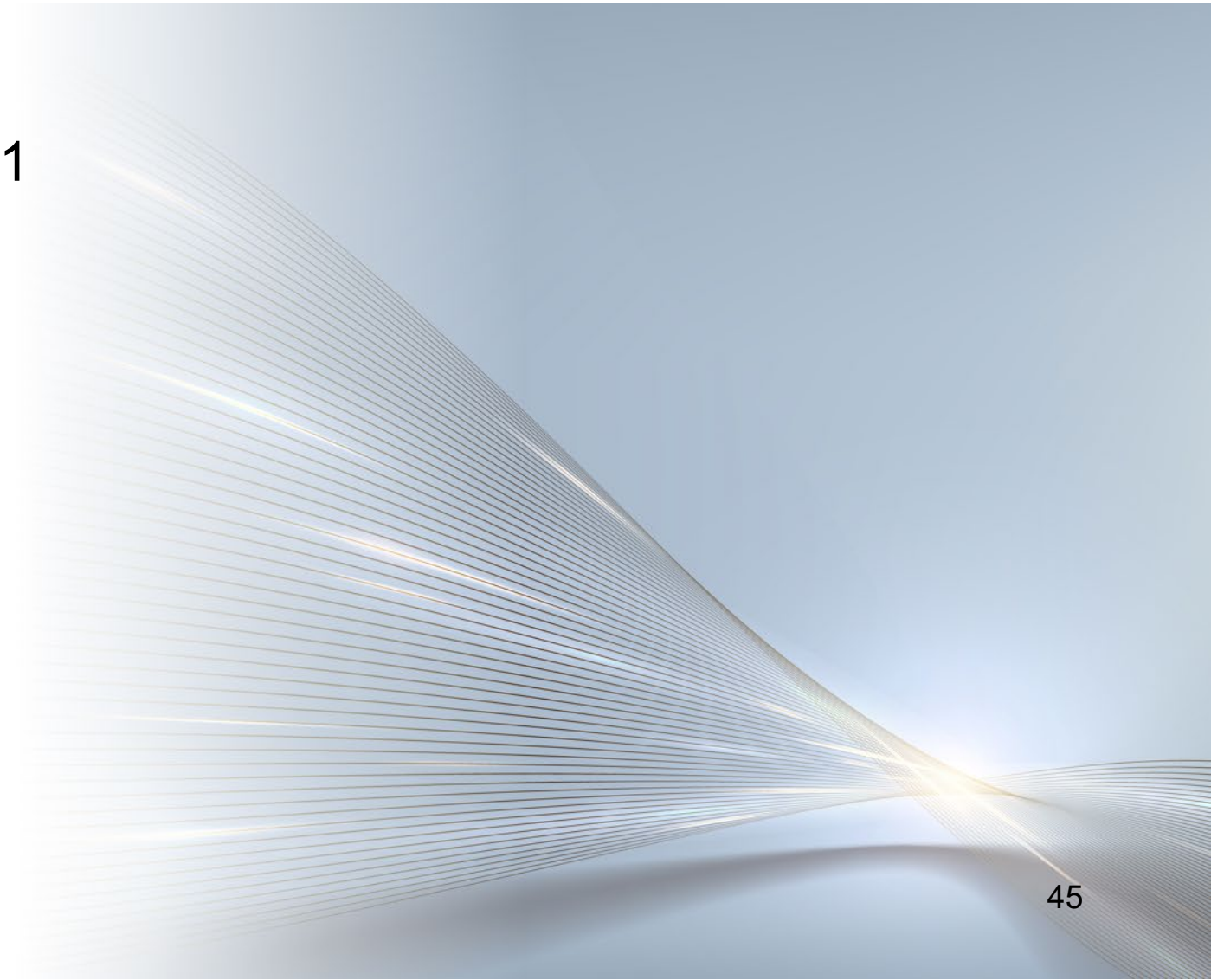
- **FDA standards have not changed**
  - CDER maintains the same standards for BLAs and inspections
- **CDER is approving more BLAs than ever before**
  - 2023 had the highest number of BLA approvals ever
  - BLA submissions are rising overall



- **Complete Response Letters (CRs) are also rising**
  - CRs across all disciplines (CMC, clinical & others)
  - BLAs were CR'ed nearly half the time in 2023
  - Resubmissions can account for multiple CRs

FDA Modernization & Unified Compliance

- FDA reorganization Launched Oct. 1
- New model for field operations
- Streamlines compliance functions within CDER
- New processes and procedures needed to ensure a seamless transition to the new structure



Drug Supply Chain Security Act

- October 9 - DSCSA Exemptions from Section 582(g)(1) and Other Requirements of the FD&C Act for Certain Trading Partners
- FDA recognizes that trading partners, who have initiated their systems and processes and have established electronic DSCSA data connections with their trading partners need more time to strengthen capabilities to mitigate data issues associated with electronic DSCSA transaction information and transaction statements and to ensure uninterrupted product distribution.
- FDA exemptions to accommodate the additional time beyond November 27, 2024, that may be needed by trading partners who have initiated their systems and processes, including electronic DSCSA data connections, to strengthen capabilities to address challenges with data exchange, quality and reliability

Final Thoughts

- Medicines only work if patients have access
- The generic and biosimilar industries have made outstanding contributions to public health by increasing access and affordability
- Attention to quality manufacturing at all levels of the organization is key to maintaining supply and confidence
- We look forward to continuing to innovate with you to bring to generic and biosimilar drugs to the market and maintain them on the market through quality manufacturing

Thank You!

& thank you to
the talented staff in the
Office of Therapeutic Biologics and Biosimilars
Office of Generic Drugs
Office of Pharmaceutical Quality


FDA
U.S. FOOD & DRUG
ADMINISTRATION