State of Generics and Biosimilars 2024

Center for Drug Evaluation and Research
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FDA U.S. FOOD & DRUG ADMINISTRATION

Disclosures

- No financial disclosures

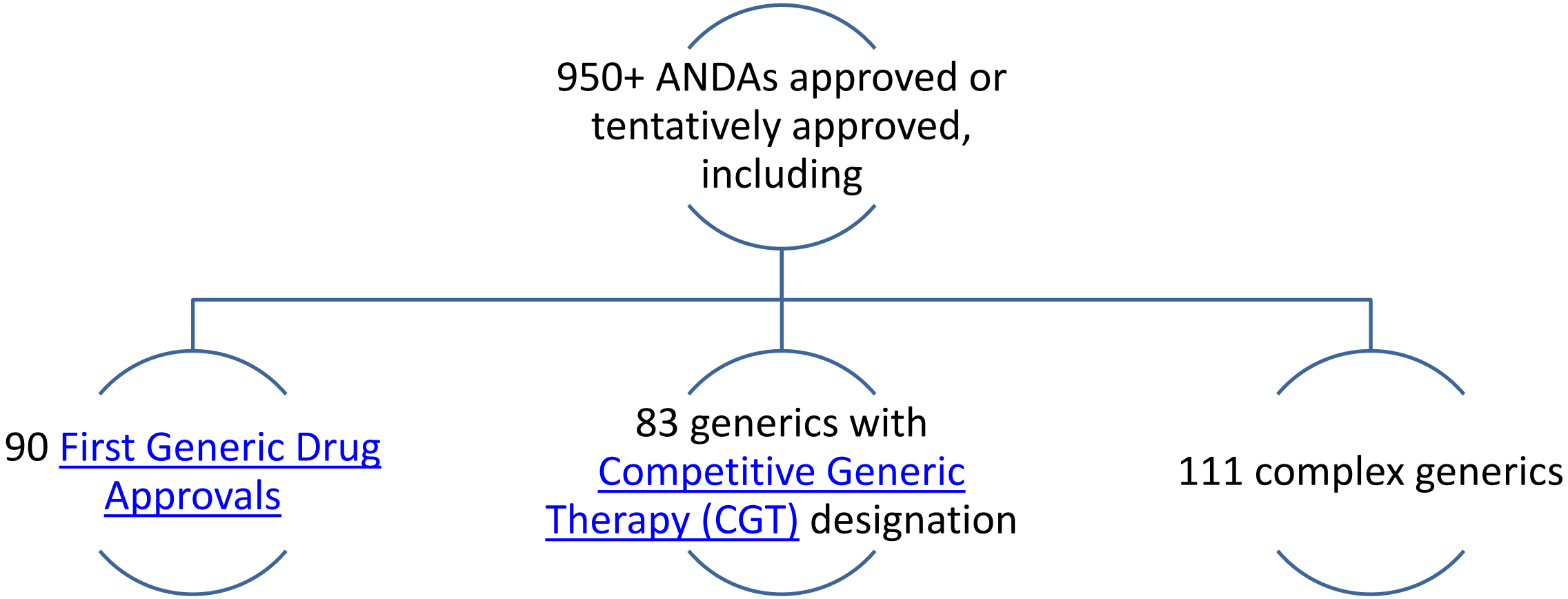
- This presentation represents the views of the speakers and not necessarily those of FDA

Overview

- A snapshot of where we are today
- Driving Innovation through Regulatory Science
- Communication is key
- International Convergence
- Opportunities

FDA Generic Drug Program

Calendar Year (CY) 2023 Generic Approvals



CY23 Examples of First Generics

Generic Name	Brand Name	Indication	Approval Date
Tofacitinib Tablets	Xeljanz	Rheumatoid arthritis; psoriatic arthritis; ulcerative colitis	3/13/2023
Obeticholic Acid Tablets	Ocaliva	Primary biliary cholangitis	5/30/2023
Tiotropium Bromide Inhalation Powder	Spiriva HandiHaler	Chronic obstructive pulmonary disease (COPD)	6/20/2023
Naltrexone for Extended-Release Injectable Suspension	Vivitrol for Extended-Release Injectable Suspension	Prevention of relapse to opioid dependence	7/6/2023
Plerixafor Injection	Mozobil Injection	Stimulating factor to mobilize hematopoietic stem cells	7/24/2023
Saxagliptin Tablets	Onglyza	Type 2 Diabetes	7/31/2023
Lisdexamfetamine Dimesylate Capsules and Tablets	Vyvanse	Attention Deficit hyperactivity Disorder; Binge eating disorder	8/25/2023
Teriparatide Injection	Forteo	Osteoporosis	11/16/2023

GDUFA III FY23 Performance Metrics

FDA U.S. FOOD & DRUG ADMINISTRATION

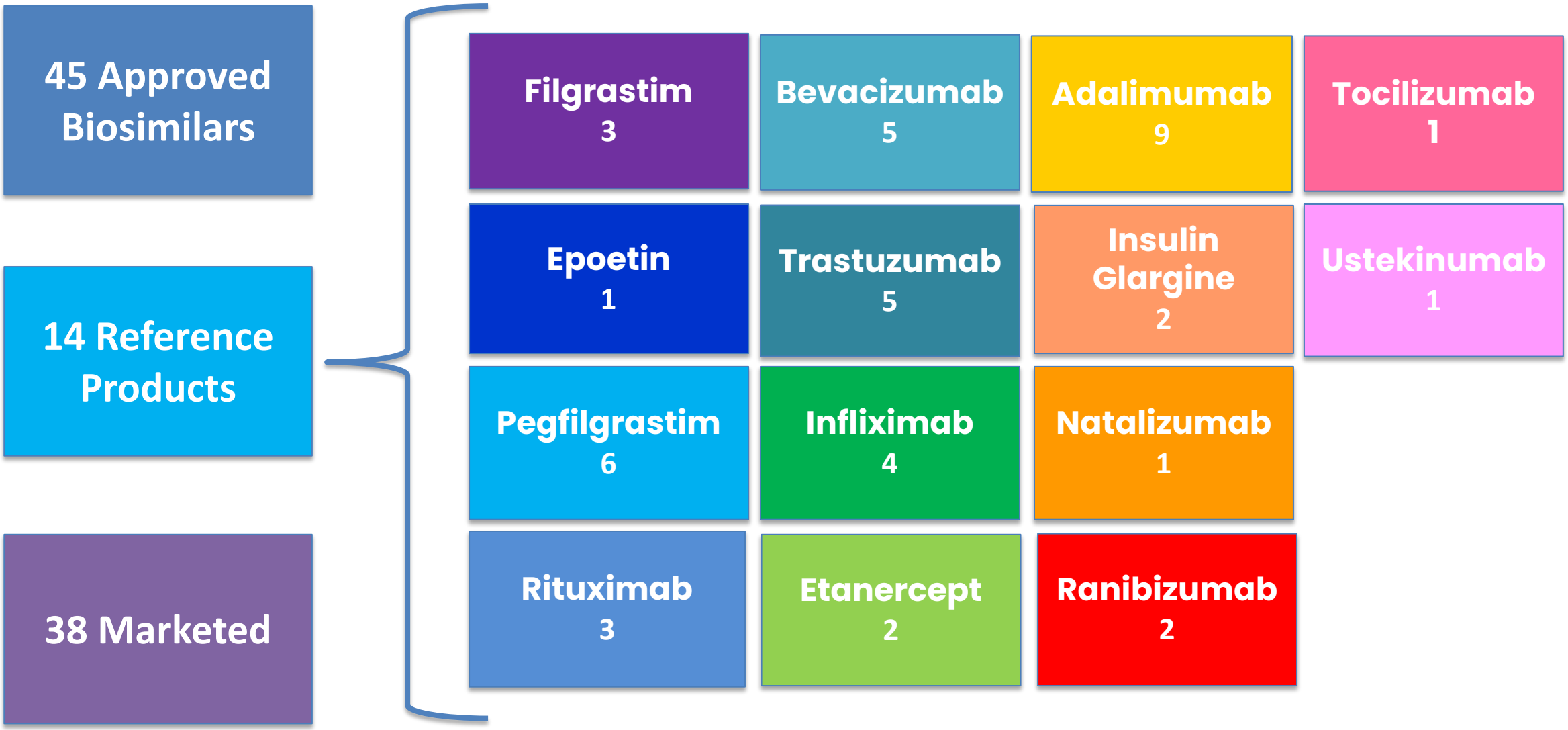
	Review Time Goal	Actions Completed	Percent Completed on Time	Potential Range	On-Time Imminent Action +	Imminent Action Potential Range ++
Original ANDA Review						
Standard Original ANDA Submissions	10 months	76 of 511	93%	15% to 99%	100%	15% to 100%
Priority Original ANDA Submissions (if applicant meets requirements of a PFC)	8 months	8 of 24	78%	29% to 92%	100%	33% to 100%
Priority Original ANDA Submissions (if applicant does not meet the requirements of a PFC)	10 months	19 of 115	100%	17% to 100%	100%	17% to 100%
Standard and Priority Original Facility not Ready with Reset	30 months	0	--	--	--	--
Amendment Review						
Standard Major ANDA Amendments (if PAI is not required)	8 months	227 of 720	92%	31% to 99%	97%	31% to 99%
Standard Major ANDA Amendments (if PAI is required)	10 months	10 of 46	50%	13% to 86%	90%	20% to 98%
Priority Major ANDA Amendments (if PAI	6 months	57 of 116	93%	47% to	95%	48% to 97%

Generic Drugs Program Activities Report - FY 2023
Monthly Performance

ACTIONS BY MONTH	Oct-22	Nov-22	Dec-22	Jan-23	Feb-23	Mar-23	Apr-23	May-23	Jun-23	Jul-23	Aug-23	Sep-23	FY-2023
Supplements	693	727	676	688	727	921	839	1183	1012	874	916	979	10235
CBE	584	574	566	591	623	757	712	986	866	754	775	846	8634
PAS **	109	153	110	97	104	164	127	197	146	120	141	133	1601
Controlled Correspondence ***	267	303	277	286	296	378	278	349	313	325	284	312	3668
Level 1	235	280	253	255	271	336	240	314	280	294	249	276	3283
Level 2	32	23	24	31	25	42	38	35	33	31	35	36	385

FDA Biosimilars Program

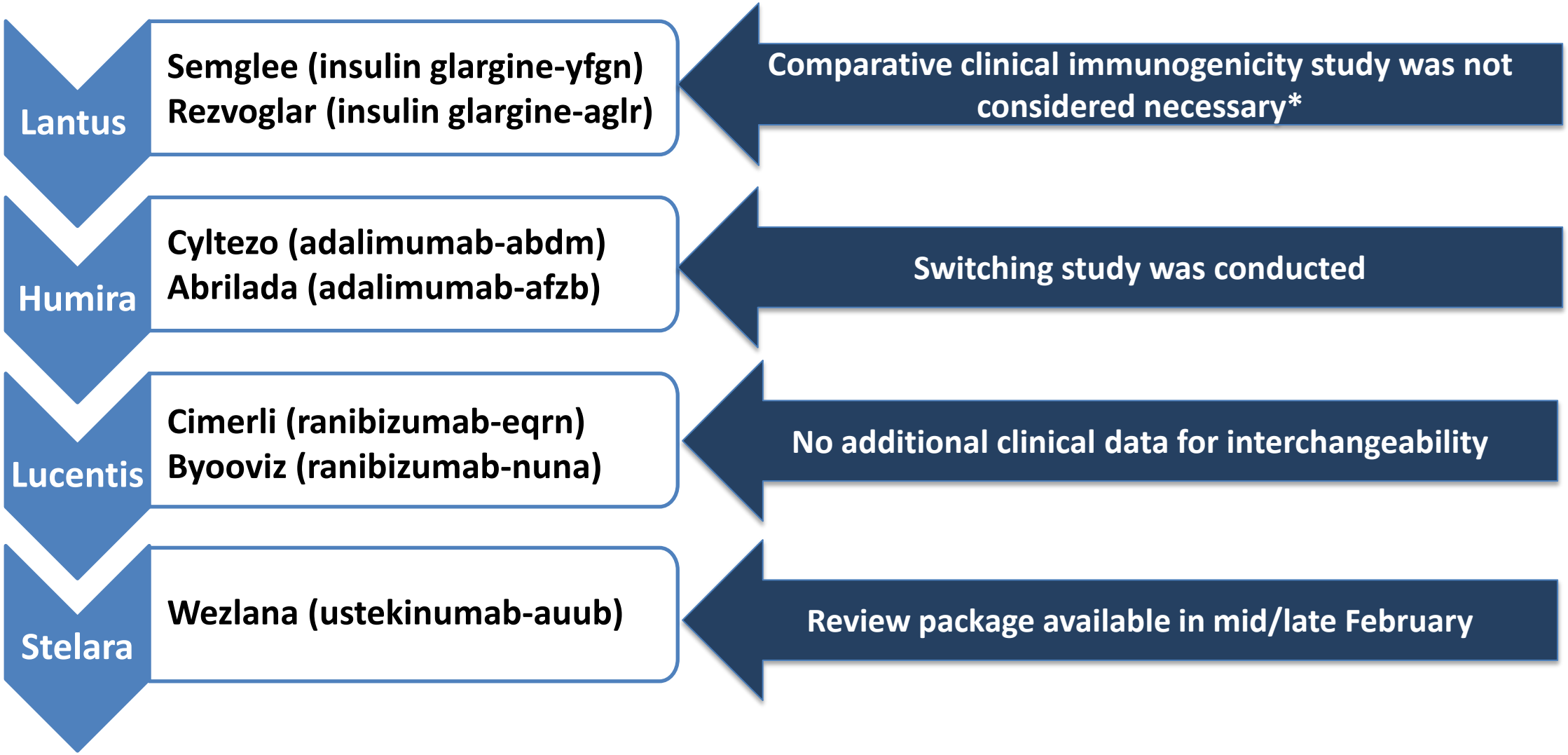
FDA Approved Biosimilar and Interchangeable Biosimilars



As of December 6, 2023

Interchangeable Biosimilars

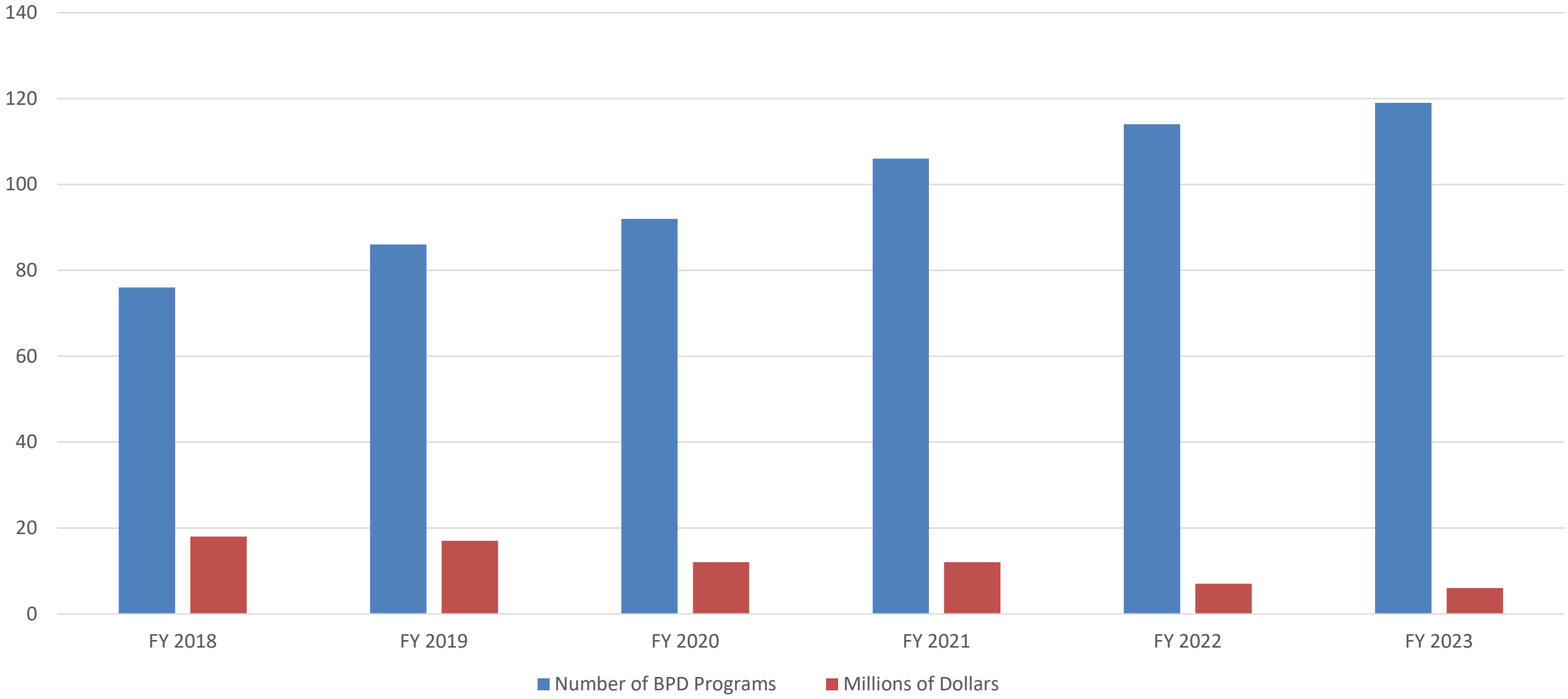
To date, FDA has approved seven interchangeable biosimilars to four different reference products



*Draft Guidance for Industry: Clinical Immunogenicity Considerations for Biosimilar and Interchangeable Insulin Products, 2019 https://www.fda.gov/media/133014/download

Review Documents available at: Drugs@FDA: FDA-Approved Drugs

Biosimilar Biological Program Development



Science Drives Policy
Generics

2023 GDUFA Science and Research Projects

- **9** new grants and **11** new contracts
  - **10** ongoing grants and **21** ongoing contracts
- **76** ongoing external research collaborations
- **70** peer-reviewed articles
  - Generic content featured in FDA's Impact Stories/Spotlights on CDER Science
- **172** external presentations
- **96** posters at scientific and medical conferences

FY 2024 Generic Drug Science & Research Priorities

- Develop methods for generics to address impurities, such as nitrosamines
- Enhance the efficiency of bioequivalence approaches for
  - complex active ingredients
  - complex dosage forms and formulations
  - complex routes of delivery
  - complex drug-device combination products
  - oral and parenteral generic products
- Facilitate the utility of model-integrated evidence to support demonstrations of bioequivalence
- Expand the use of artificial intelligence and machine learning tools

MIE Industry Meeting Pilot

Launch Date: October 1st, 2023

Mission:

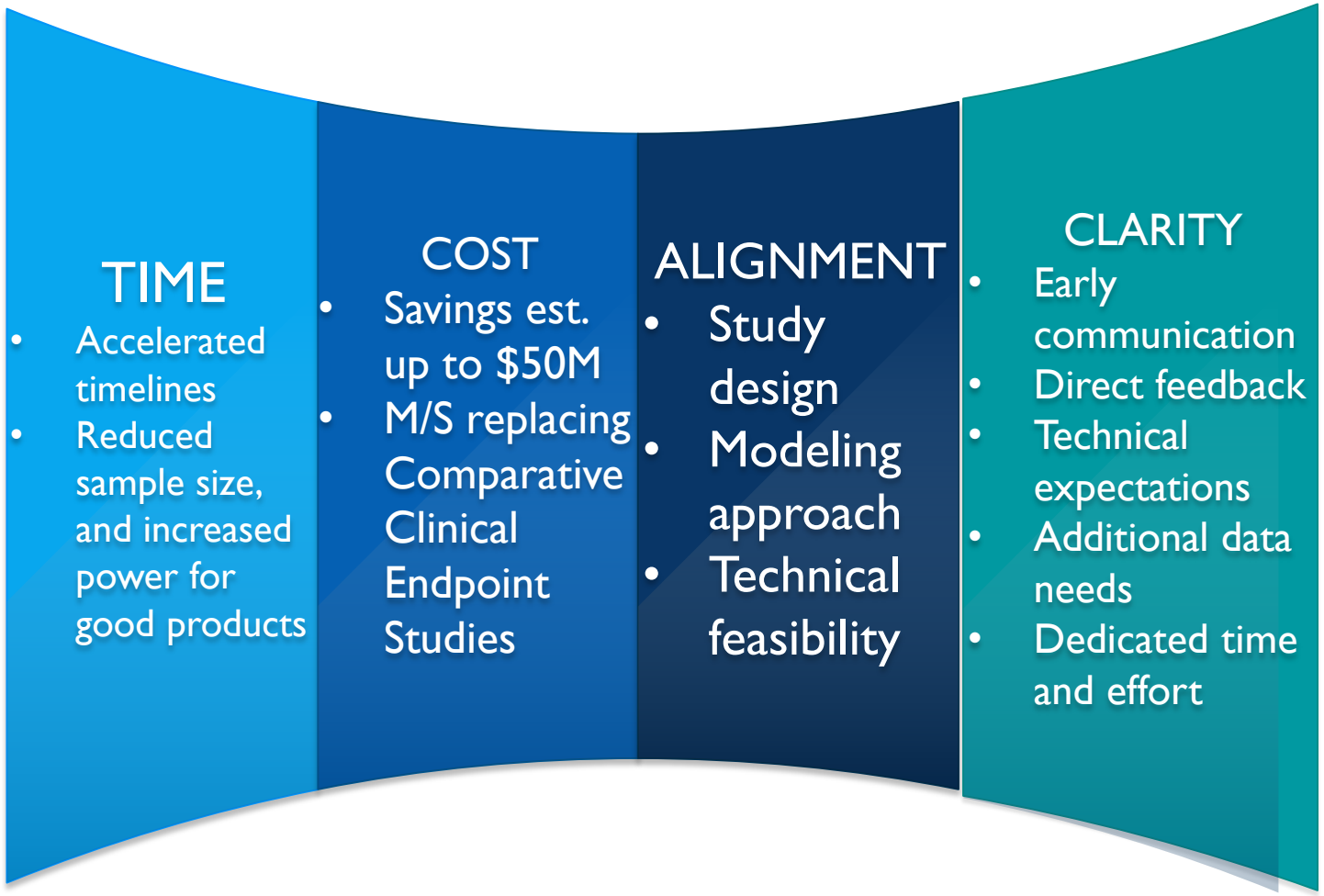
This new pilot program is to provide industry with meetings and opportunities for early interaction for science-driven topics using model-integrated evidence (MIE) approaches for bioequivalence (BE) establishment to facilitate generic drug development and regulatory decision making.

Specifically, the pilot MIE meeting(s) will focus on discussing scientific and technical topics of using MIE strategies for BE establishment (e.g., feasibility, details in model building, and/or model verification and validation data) while pre-ANDA meetings will be focused on more general scientific and regulatory issue(s).

General Principles Document: https://www.fda.gov/media/172028/download?attachment

Potential Impacts and Benefits

Industry Benefit →



Agency Benefit ↓

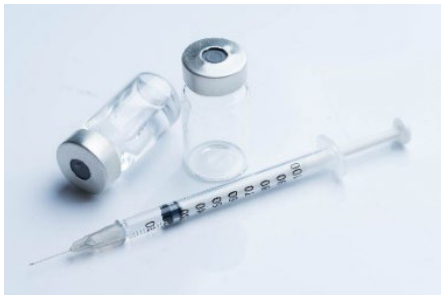
- Efficiency to handle multiple products
- Reducing number of cycles for drug approval
- Eco-system with industry to develop effective BE approaches

Eligibility Criteria for MIE-Pilot

- Under the MIE Pilot Program, a meeting may be granted if it pertains to:
  - innovative MIE-focused approaches for BE establishment that cannot be effectively addressed under the existing GDUFA scientific meetings,
  - non-complex products with complex approaches/modeling for Biopharmaceutics Classification System (BCS)--based biowaivers and/or other study waivers, and
  - novel data analytics tools and approaches (e.g., machine learning and artificial intelligence) for BE establishment and assessment.

Key Operational Aspects

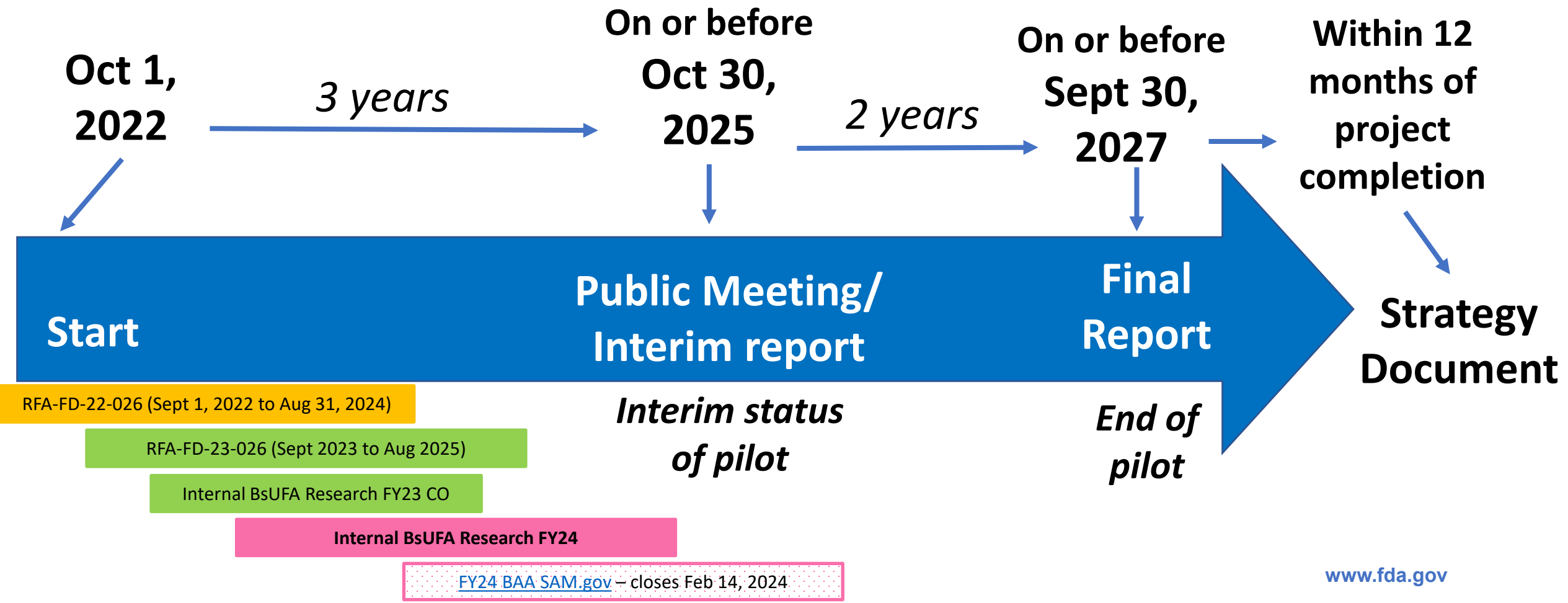
- Post its launch on October 1st, 2023 and FDA will evaluate the pilot program at the end of year one or after five meetings have been held, whichever occurs first to determine the next phase of the pilot program
- Areas of Focus
  - Locally acting products (e.g., orally inhaled and topical dermatological products), and long-acting injectables etc.



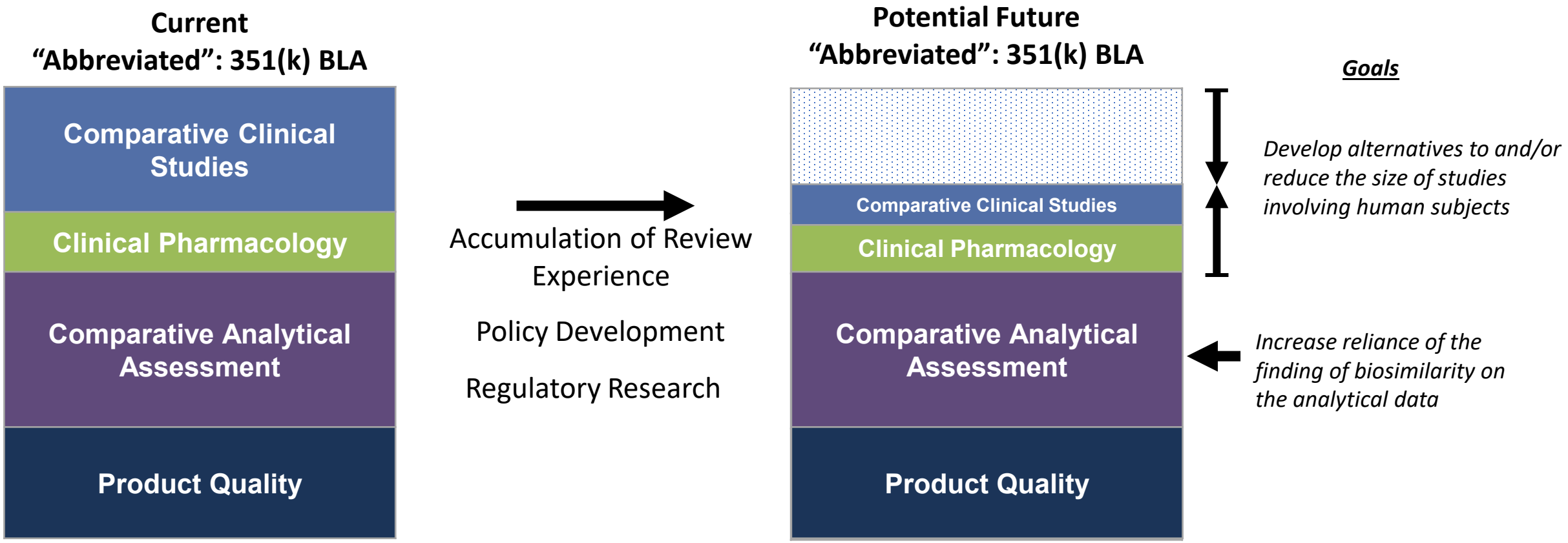

  - Non-complex products: Novel biowaiver requests supported by mechanistic modeling, and oncology products

Science Drives Policy
Biosimilars

Regulatory Science Pilot Program Deliverables



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



Feedback on Research Priorities and Draft Roadmap

- **Continuous Engagement Meetings as part of BsUFA III**
  - Continuous engagement meetings are held biannually - Regulatory Science Pilot Program discussed Feb 2023 and Nov 2023

- **<u>Public Comment Period</u> on Draft Regulatory Roadmap** (January 25 – April 5, 2023)
  - Received comments from seven stakeholder/entities

- **Ten invited talks about the Reg Sci Pilot Program (Spring/ Summer/ Fall 2023)**
  - External – Howard University, USP, AMCP, Biosimilar Forum, SBIA REDi Conference, BAA Day
  - Internal – CDER RGC, CDER IRC

SBIA Webinar and In-Person Round Table

- **SBIA Webinar on October 16, 2023** BsUFA III Regulatory Science Pilot Program - 10/16/2023 | FDA
  - FDA updated and engaged with almost 400 stakeholders about program progress

- **In-person Round Table Discussion on October 26th**
  - 20 stakeholders and FDA staff discussed recommendations to improve regulatory impact of demonstration projects under revised research priorities
  - Developed summary report about the discussions
  - Received positive feedback about the round table format:
    - Most participants found the meeting to be very informative
    - All participants would be in favor of similar in-person events

Summary Report: http://www.fda.gov/media/174044/download?attachment

Research Priorities That Result in Regulatory Impact

a. Characterize relationships between product quality attributes (physiochemical or biological) with clinical performance

b. Explore how modernization of analytical technologies could better and/or more efficiently detect relevant quality attributes

c. Define best practices for assessing and reporting quality attributes

d. Develop alternatives to the comparative clinical immunogenicity assessment(s)

e. Define approaches that will increase feasibility of biosimilar development (e.g., PD biomarkers, modeling and simulation)

f. Identify user interface differences that will likely lead to clinically meaningful differences in use error rates or use success rates

Achieving Regulatory Impact from the Demonstration Projects

1. Increase the reliance on analytical data in a demonstration of biosimilarity

2. Develop alternatives to and/or reduce the size of studies involving human participants

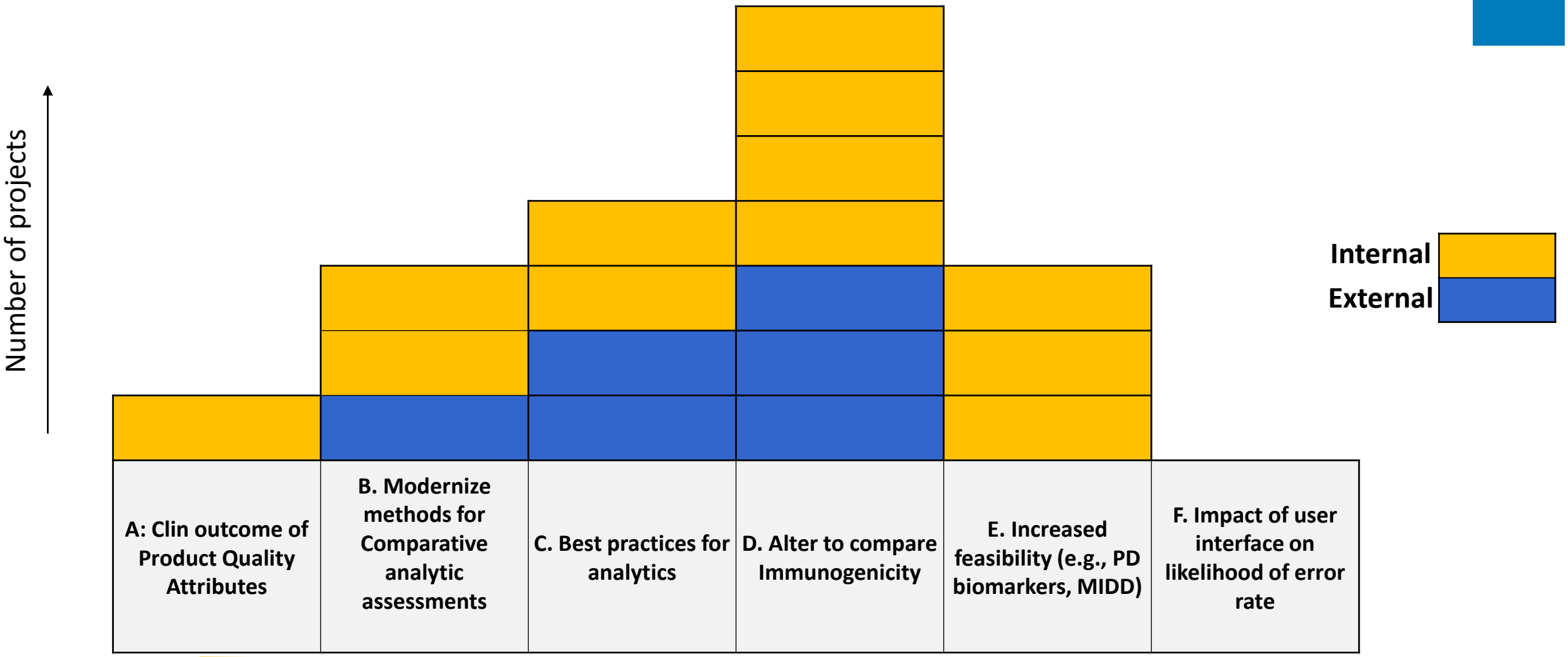
Demonstration Projects from BsUFA III

- Advance the development of interchangeable products
- Improve the efficiency of biosimilar product development

Methods to Consider for Research Conducted as Part of the Pilot Program

- Analytical methods
- Biological assays
- Efficient clinical design (e.g., statistical methods)
- In silico/in-vitro modeling
- MIDD applications
- Machine learning/artificial intelligence
- Pharmacological studies
- RWE/RWD

Research Priorities Addressed by Awarded Projects (n=18)



https://www.fda.gov/media/162361/download?attachment

Biosimilar Research Projects

Research Priority B: Explore how modernization of analytical technologies could better and/or more efficiently detect relevant quality attributes.

Total Amounted Awarded for Research Priority B: $2,598,958 USD.

2. **Assessment of the performance of Multi-Attribute Method (MAM) vs conventional Quality Control (QC) methods for evaluation of Product Quality Attributes of adalimumab and etanercept**

   Institute: U.S. Pharmacopeia
   Principal Investigator: Diane McCarthy
   Expected Timeline for Project Completion: 2 years from Fall 2022

   Selection from Abstract from Grant Application: Monoclonal antibodies and other biotherapeutics are subject to a variety of modifications that can impact activity and stability and therefore must be analyzed as part of QC and comparability. Mass spectrometry (MS) has become a workhorse for biopharmaceutical analytical laboratories due to its ability to detect protein modifications at a molecular level. Over the past few years, the Multi-Attribute Method (MAM) has gained traction throughout pharmaceutical development and QC labs, with several developers implementing some form of MAM in characterization or release. While replacing

https://www.fda.gov/drugs/biosimilars/biosimilars-science-and-research

Transparency and Communication about the Pilot Program

- **Published three annual reports for RFA-FD-22-026**
  - three of five awardees granted permission for July 2023 reports - https://www.fda.gov/media/162361/download?attachment

- **Invited non-FDA grant reviewers for RFA-FD-23-026**
  - four individuals indicated interest; three were included in reviewer nominations
  - two served as reviewers on three different applications

- **Published full research portfolio with both internal and external research projects**
  - 18 projects total – 12 internal and 6 external (https://www.fda.gov/media/162361/download?attachment)

BsUFA III Reg Sci Program Operational Structure & Decision Making

Strategic and Final Input

CDER Leadership - Final funding decisions on research portfolio

Regulatory Science Evaluation

Discipline SMEs - Evaluates and oversees research portfolio

Regulatory Science Pilot Program

Program Management - Provides individual project tracking

Office of Acquisition and Grant Services (OAGS)

Grants 101 | GRANTS.GOV

FDA Project Officers

External Grants

Internal Projects

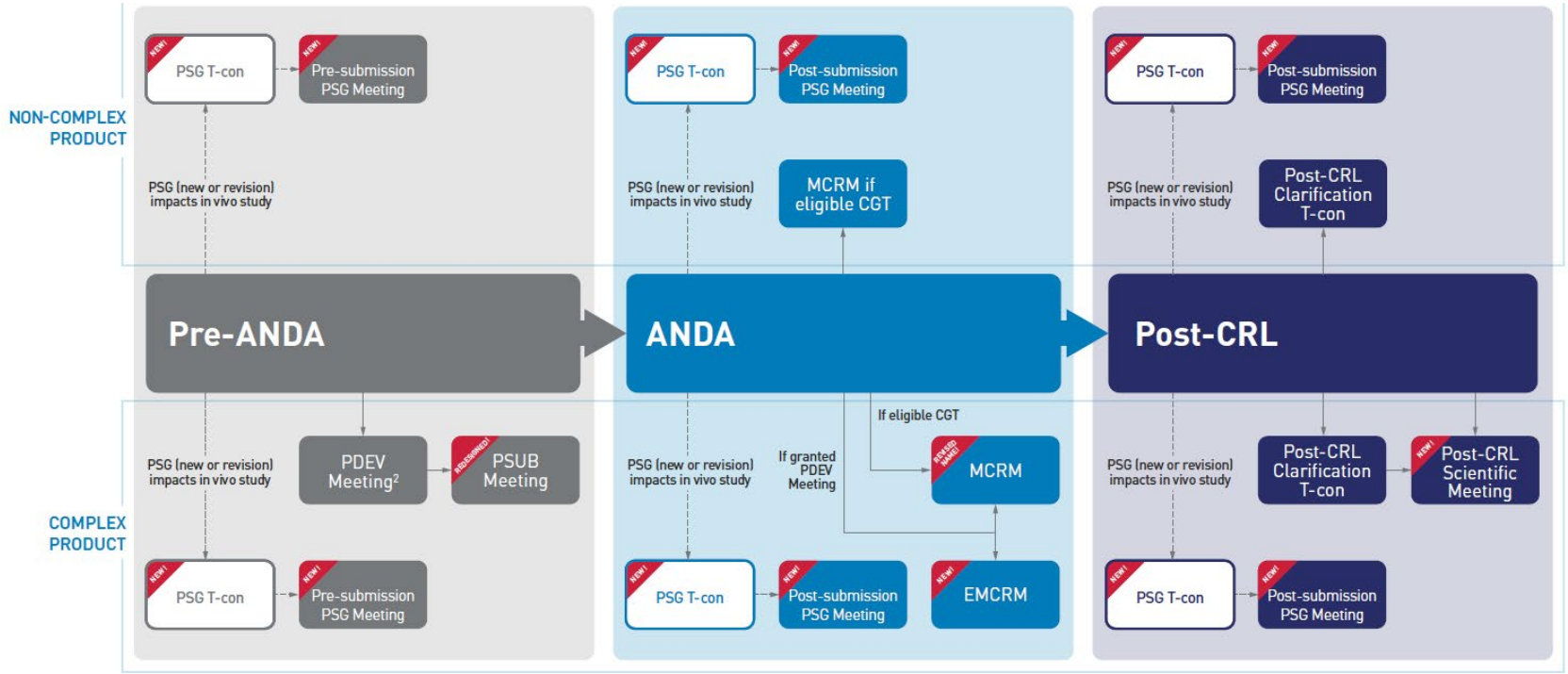
Internal review process

GDUFA III – Facilitating Communication

Examples of GDUFA III Enhancements

- Goal dates for product-specific guidances (PSGs) after a complex product for a New Drug Application
  - First goal dates - October 2024
- Product-Specific Guidance Meetings
- ANDA assessment team members included in pre-submission meetings
  - Helps the ANDA assessment team better understand the application

GDUFA III Meetings and Teleconferences



PSG teleconferences: applicants receive FDA feedback on the potential impact of a new or revised PSG on the applicant's ANDA development program

PSG meetings: applicants can discuss scientific rationale for an approach other than that recommended in the PSG, to ensure approach complies with FDA statutes and regulations

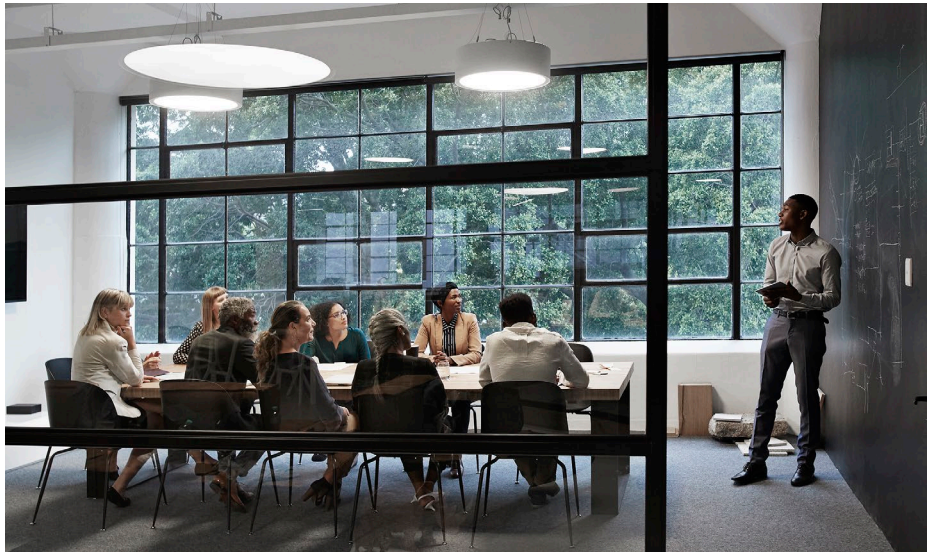
GDUFA In-Person Meetings

In-person face-to-face (FTF):

1. pre-ANDA product development
2. pre-submission meetings
3. pre-submission product-specific guidance (PSG) meetings
4. post-submission PSG meetings
5. enhanced mid-cycle review meetings
6. post-complete response letter (CRL) scientific meetings

Videoconference format for:

1. PSG teleconferences (t-cons)
2. mid-cycle review meetings
3. post-CRL clarification t-cons



Communication from Applicants

- **Submit a clear cover letter**
- **Respond thoroughly**
  IRs, DRLs, and CRLs
- **Monitor updates**
  Track changes to RLD, USP, guidances, Orange Book
  - e.g., Nitrosamine Guidance
- **Submit litigation-related updates in a timely manner**
- **Remain in good standing**
  Avoid data integrity issues
- **Coordinate DMF changes**
  Avoid hidden facilities
- **Pay attention to patents**
  Address all patents in the Orange Book

BsUFA III – Facilitating Communication

BsUFA Meeting Management

- **Modifies the BIA meeting so preliminary comparative analytical data is no longer required to meet with FDA.**
  - *As of 9/30/23: 11 meetings, compared to 9 in FY22 = ~same

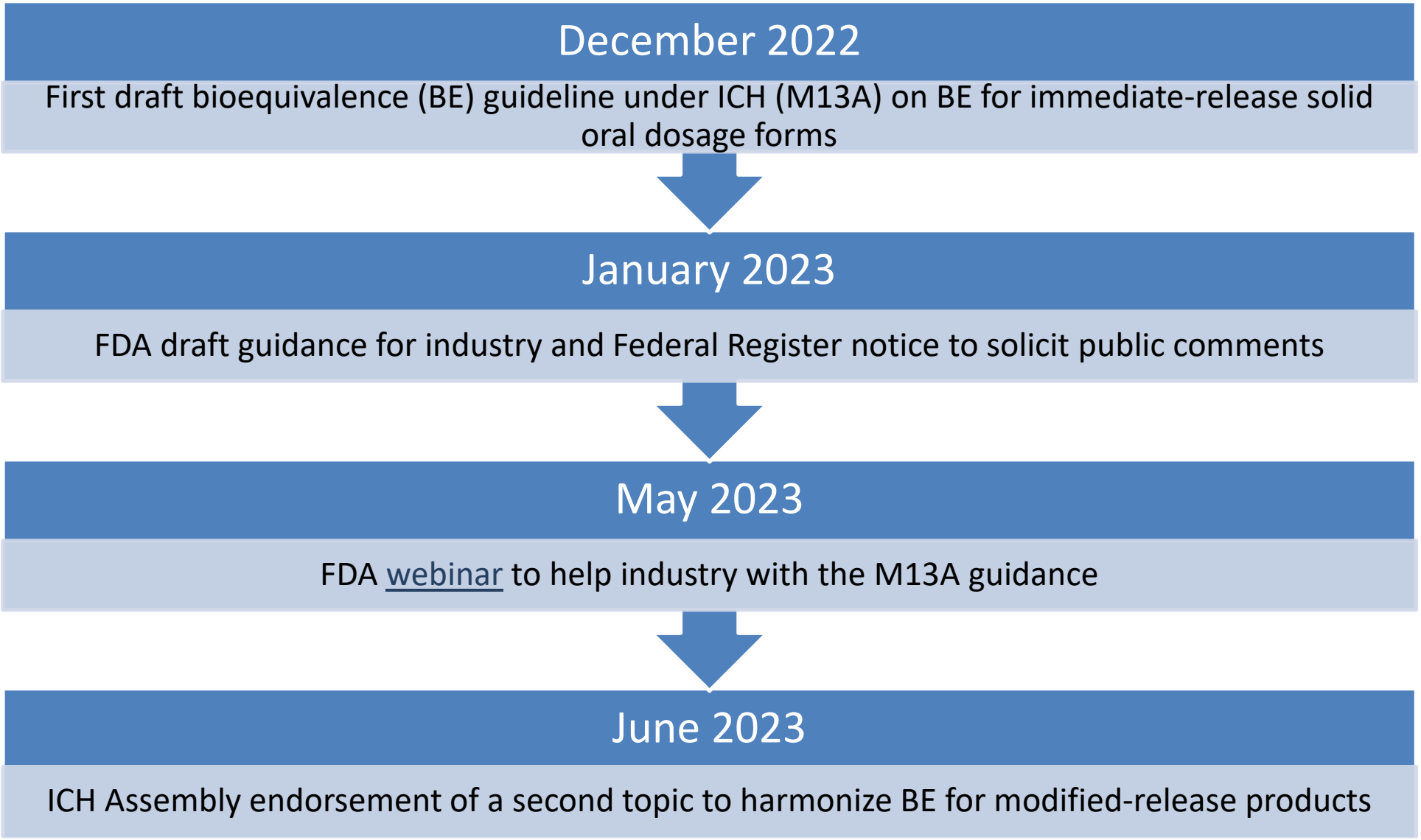
- **Introduces a new Biosimilar Product Development meeting type: Type 2a, focused on a narrow set of issues**.
  - *As of 9/30/23: Type 2a = 40; Type 2b = 46 (total 86) compared to 97 Type 2 in FY22 = change did not impact numbers

- **Modifies timing of background packages for Type 4 meetings, so they may be submitted up to 14 days after FDA receipt of the written meeting request** (previously packages were submitted with the written request).
  - *As of 9/30/23: 23 BPD4 compared to 13 in FY22

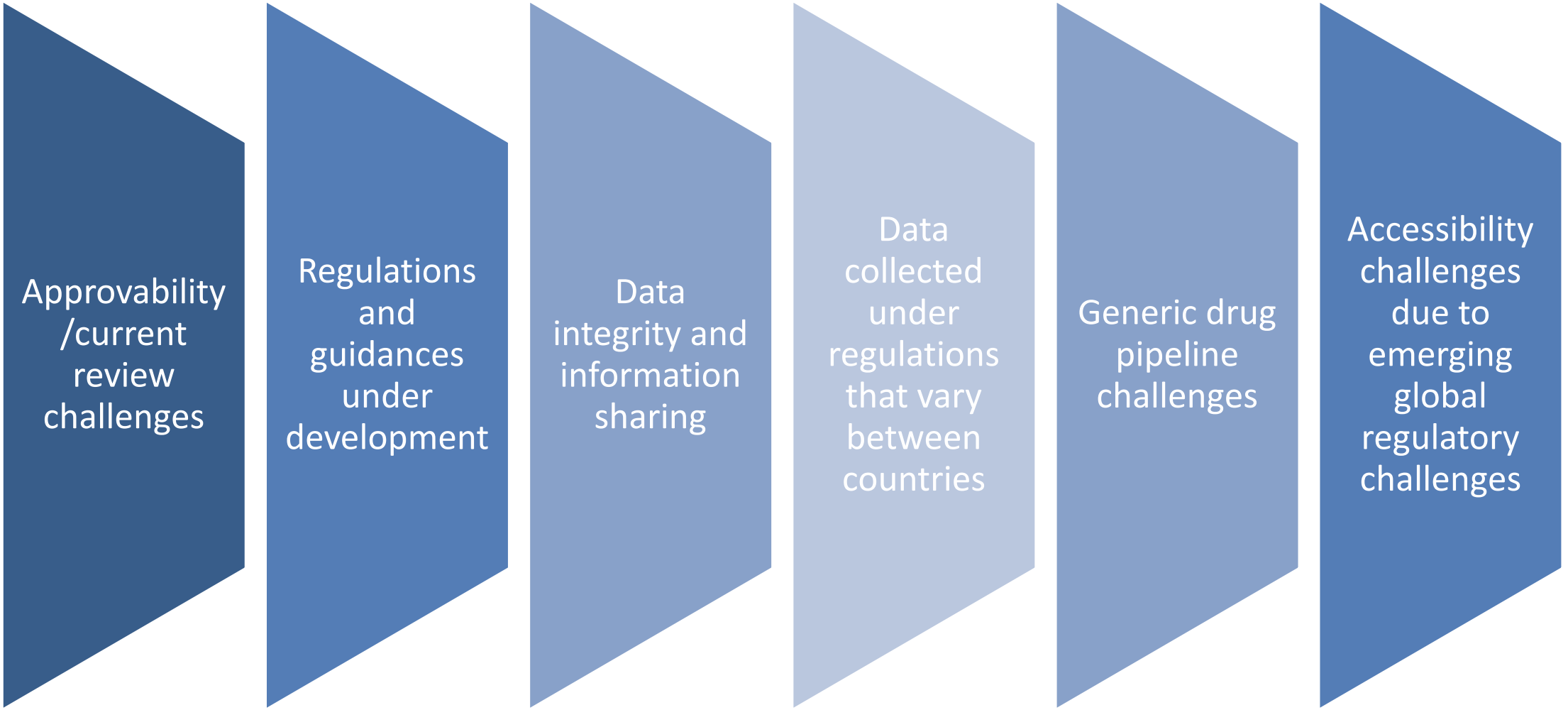
**Note: This is preliminary data and will change depending on the cohort*

Collaboration with International Regulators

Generic International Convergence Efforts



FDA Generic Drug Cluster



https://www.fda.gov/drugs/generic-drugs/global-generic-drug-affairs

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

Collaboration with International Regulators

IPRP International Pharmaceutical Regulators Programme

Biosimilar Working Group Scientific Workshop

Increasing the Efficiency of Biosimilar Development Programs—Re-evaluating the Need for Comparative Clinical Efficacy Studies

Multi-day, virtual meeting

12-13 September 2023: Public session

- Regulator and external stakeholder perspectives on the utility, challenges, costs and benefits of having comparative efficacy studies in biosimilar development programs

19-21 September 2023: Regulators only session

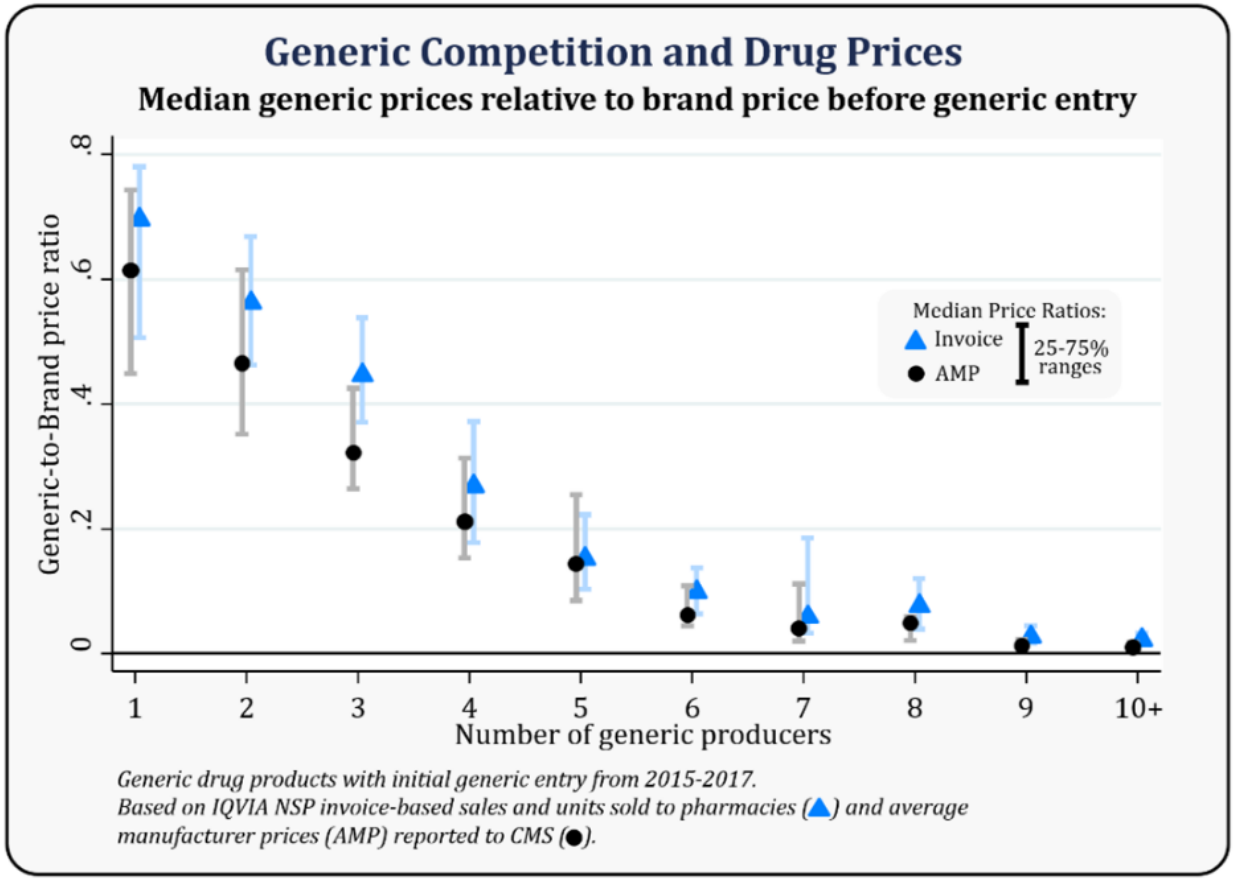
- Discuss input from the public session and a potential scientific framework for when CES may or may not be needed, along with next steps/action plan

Opportunities

Two Different Markets - Generics

- Account for 90% of prescriptions

< than 18% of prescription drug spending

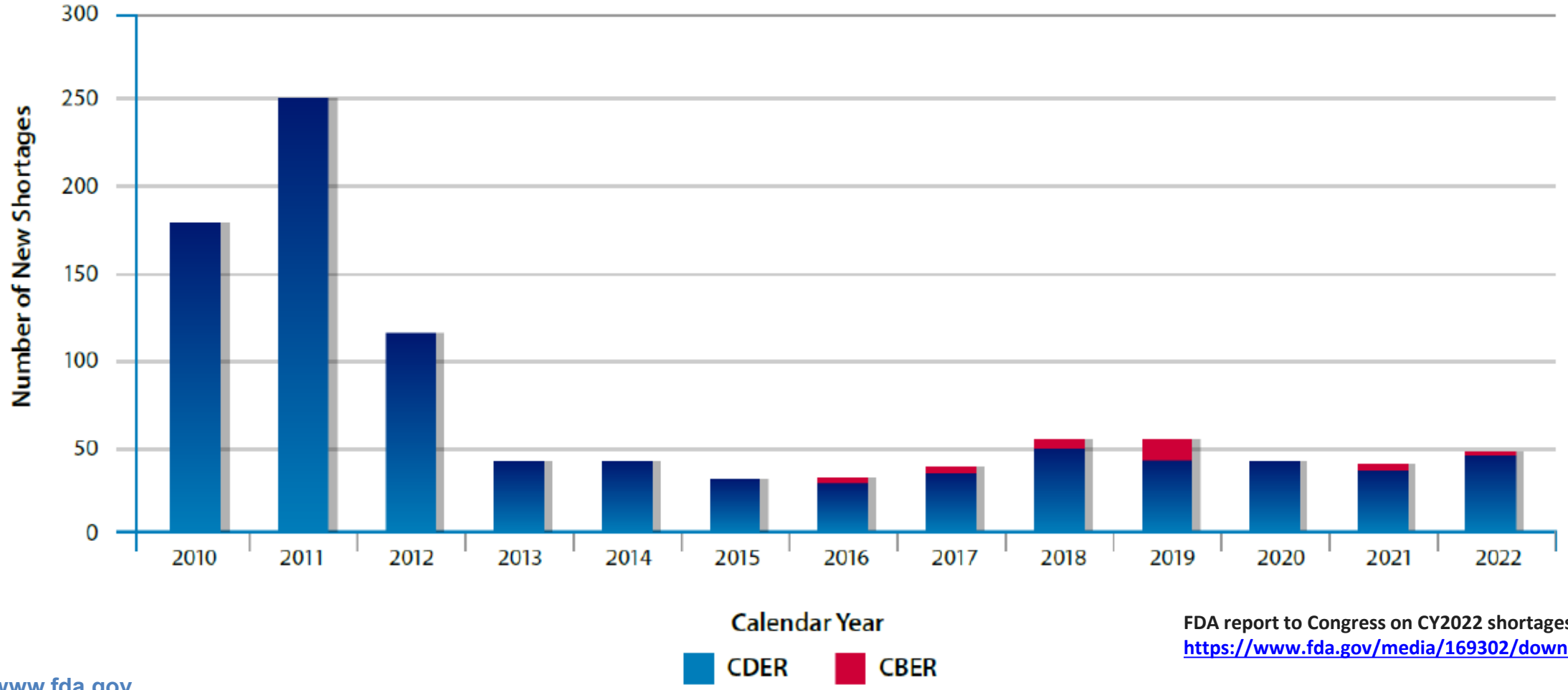


Generic Competition and Drug Prices

We recognize that there has been increasing attention on whether the lower cost of generic drugs, especially as more generics enter the market over time, may place pressure on companies to adopt strategies that lower the cost of manufacturing, which in turn may lead to supply disruptions and shortages. This paper focuses on the savings from generic drug approvals in 2021 and this larger policy question is not the focus of this analysis.
https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/generic-competition-and-drug-prices

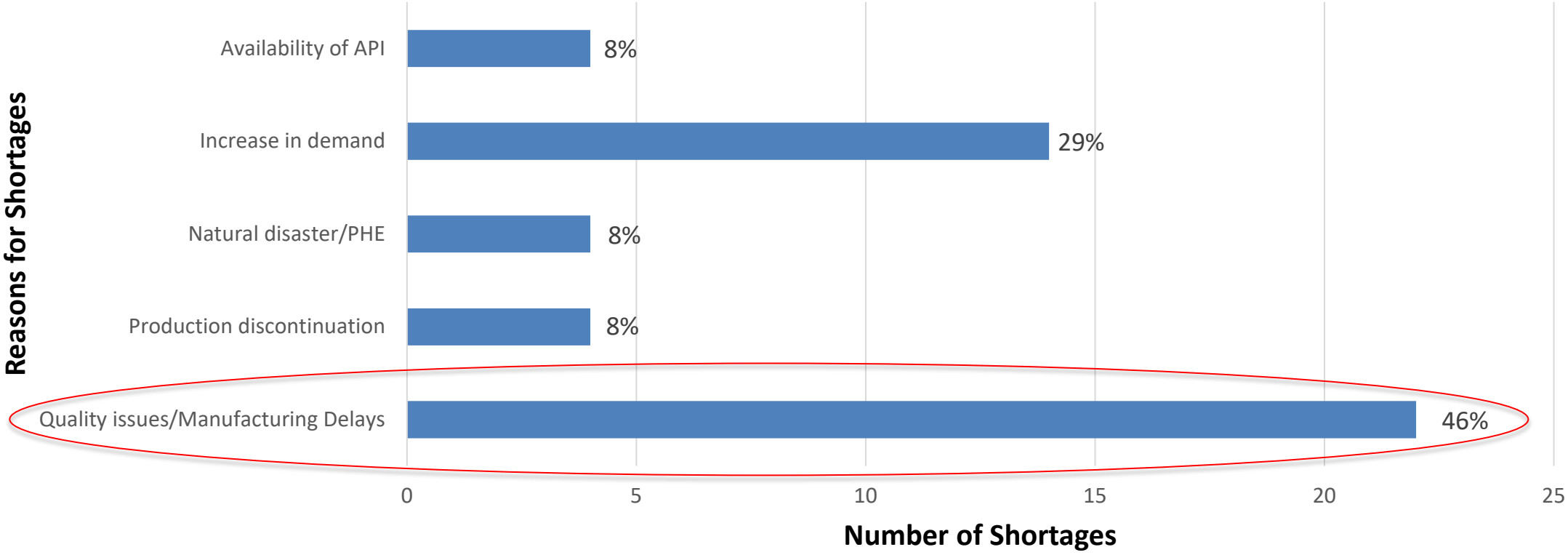
Drug Shortages

Number of New Drug Shortages Per Calendar Year



FDA report to Congress on CY2022 shortages
https://www.fda.gov/media/169302/download?attachment

Reasons for New Shortages in CY2022

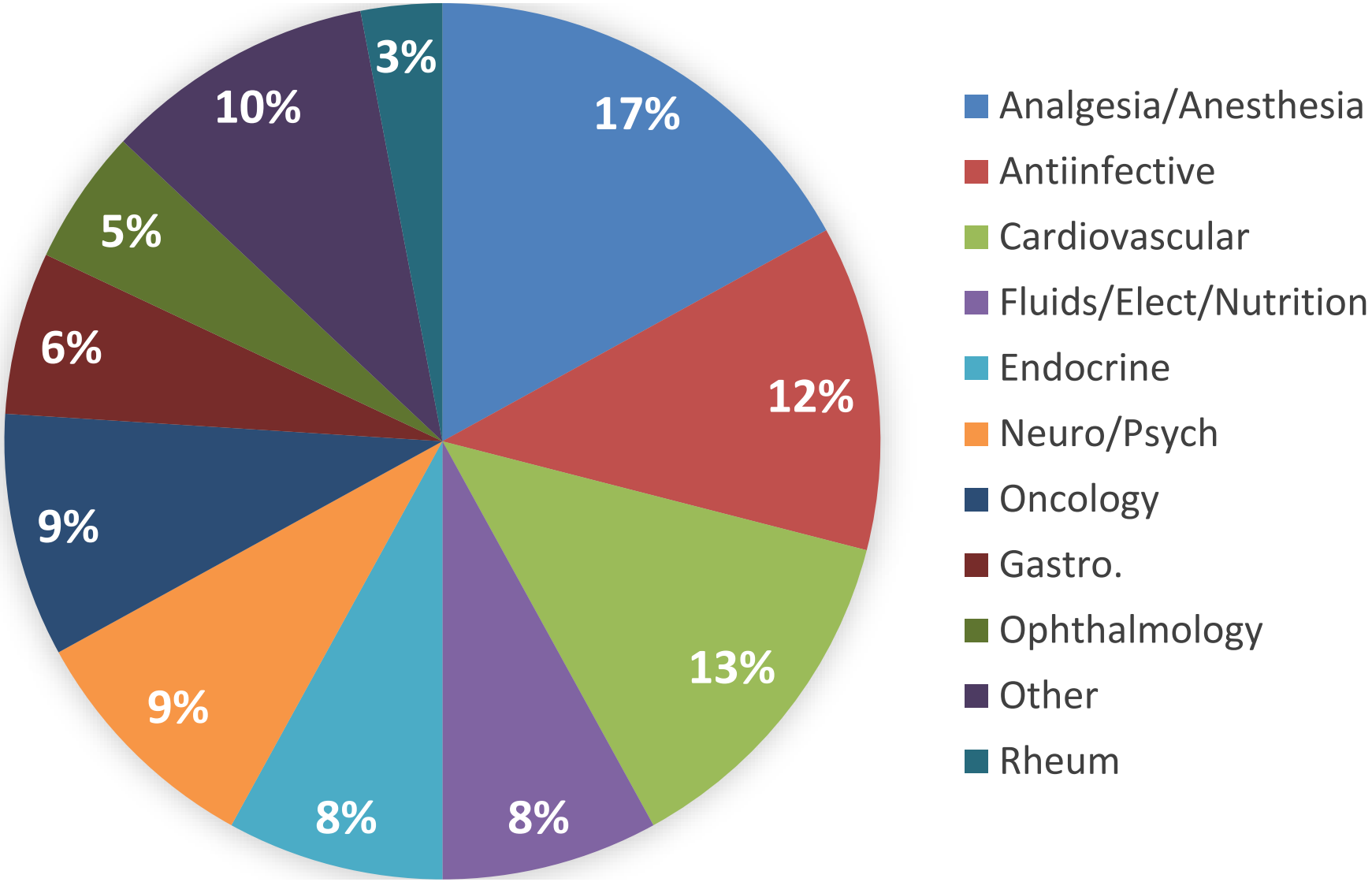


Where Are We Today

- Drugs that are currently listed in shortage as of January 27, 2023: 123 drugs
- 65% sterile injectables versus oral or topical
- Close to one-quarter were first reported before 2020, with the oldest first being reported in 2012
- Looking at a sample of 100 drugs for which shortages have resolved in the past few years, the average time to resolution was about 20 months, with the shortest listed as 1 month and the longest as just over 7 years
  - Overwhelming majority took more than 5 months to resolve

Percentage of Shortages by Clinical Indication

OTHER includes:
Hematology
Medical imaging
Renal
Reproductive
Urology
Pulmonary
Dermatology



Drug Shortage Assistance Award

FDA Drug Shortage Assistance Award to provide public recognition to drug companies and manufacturers who have demonstrated a commitment to preventing or alleviating drug shortages of medically necessary drugs.

SAGENT Pharmaceuticals®

APOTEX
Canadian-Based
Global Health Company

FRESENIUS KABI
caring for life

teva

ADIENNE PHARMA & BIOTECH

hikma.

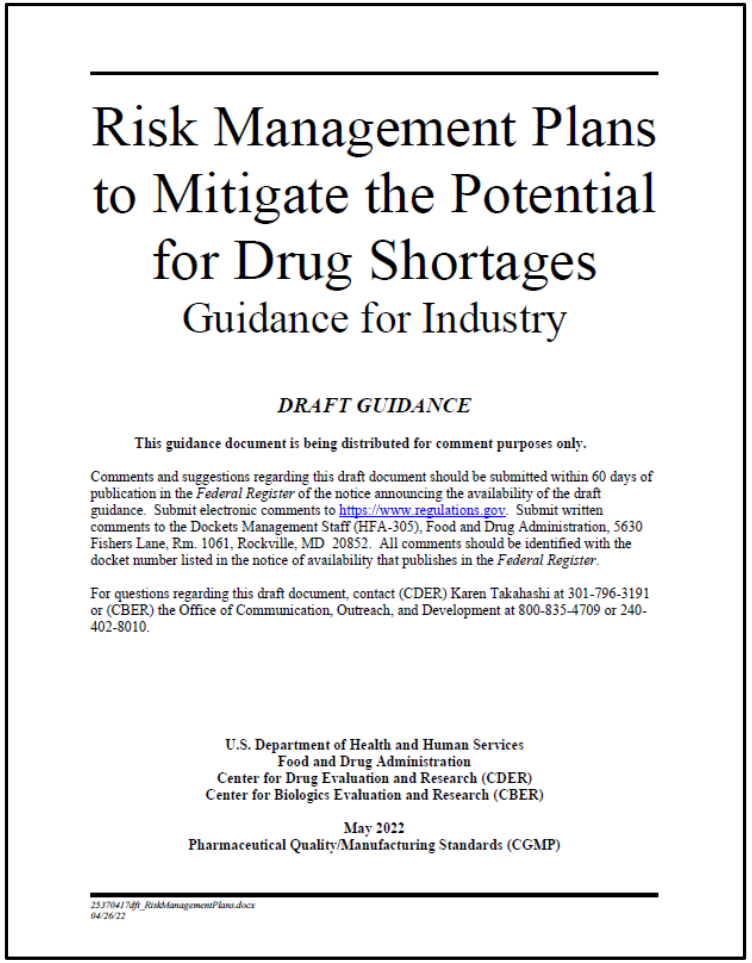
CLINIGEN

Guerbet

Eurohealth International Sarl

Risk Management Plans

- Draft guidance issued May 2022
- Intended to help stakeholders develop, maintain, and implement RMPs to proactively assist in the prevention of drug/biologic shortages
- A good business practice for most stakeholders in the supply chain
- Guidance describes a framework for stakeholders to consider when developing RMPs
  - Aligned with principles in ICH Q9
- RMPs are not expected to be routinely submitted



Risk Management Plans to Mitigate the Potential for Drug Shortages

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) Karen Takahashi at 301-796-3191 or (CBER) the Office of Communication, Outreach, and Development at 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)

May 2022
Pharmaceutical Quality/Manufacturing Standards (CGMP)

2537041?dft_RiskManagementPlans.docx
04/26/22

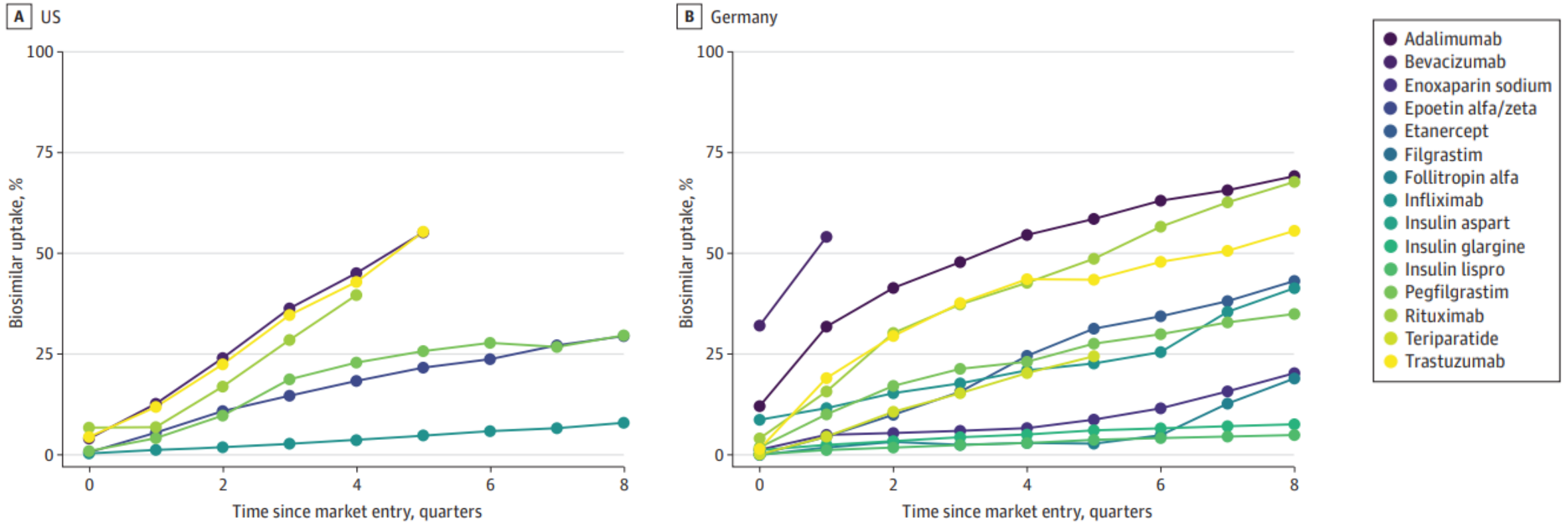
Voluntary Quality Management Maturity Prototype Assessment Protocol Evaluation Program

- **Voluntary** Quality Management Maturity Prototype Assessment Protocol Evaluation Program
- Gain experience with use of a prototype of the assessment protocol to evaluate whether use of the protocol, as currently designed, will enable a meaningful assessment of the establishment's quality management practices and actionable feedback for the establishment.
- The outcomes from this prototype evaluation program will help to inform the development of the QMM Assessment Tool

89 FR 4950

Two Different Markets – Biosimilars

Figure 1. Uptake of Biosimilars in the US, Germany, and Switzerland



Original Investigation | Health Policy

Comparison of Uptake and Prices of Biosimilars in the US, Germany, and Switzerland

David L. Carl, MSc; Yannic Laube, BA; Miquel Serra-Burriel, PhD; Huseyin Naci, PhD; Wolf-Dieter Ludwig, MD; Kerstin N. Vokinger, MD, JD, PhD, LLM

Understanding Biosimilars

Biosimilars Promotion: Digital and Social Media Outreach

HCP (Biosimilars Overview)

Prescribing Biosimilars

Learn about the FDA review and approval process for biosimilar medications.

HCP (Biosimilars Overview)

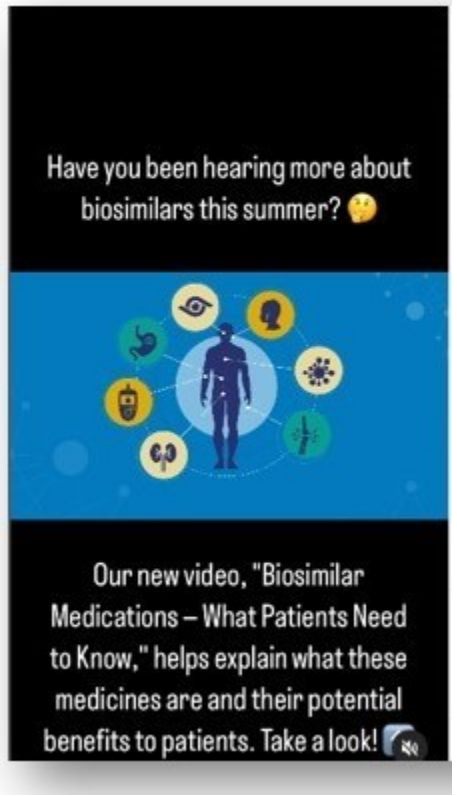
FDA Biosimilar Resources

Download the fact sheet for health care providers and explore our educational materials.

Patient

Biosimilar Basics for Patients

Brand name drugs have generic versions, original biologics have biosimilars.



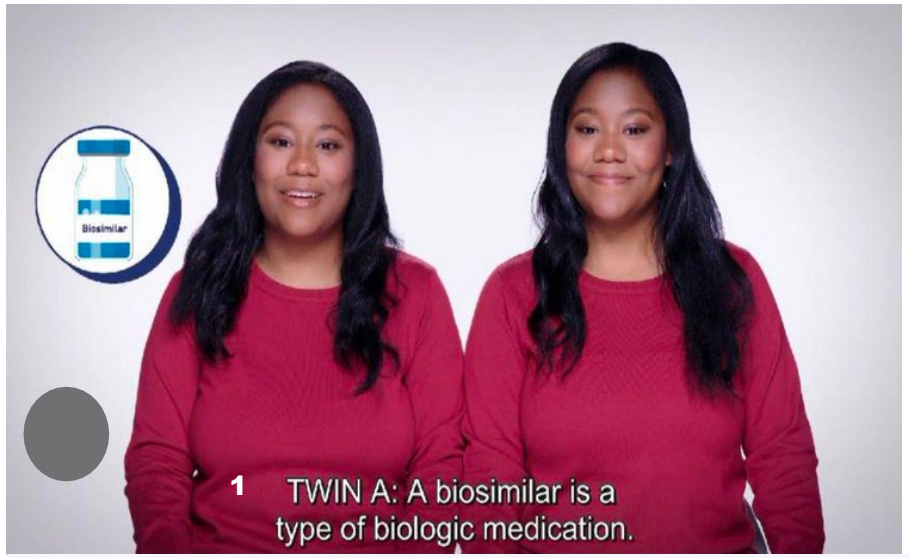
Biosimilars Promotion: Patient Waiting Room PSA

- FDA is providing information to the public on biosimilar treatment options with a new PSA featuring twins

- Placed in 750 patient waiting rooms nationwide in Rheumatology, Neurology, and Endocrinology offices
  from October-November 2023

- PSAs garnered almost 3 million impressions

- Spanish version coming soon for digital media outreach in Spring 2024



Biosimilars Promotion: MAT Article

Distribution Date:
9/8/2023

Removal Date
1/8/2024

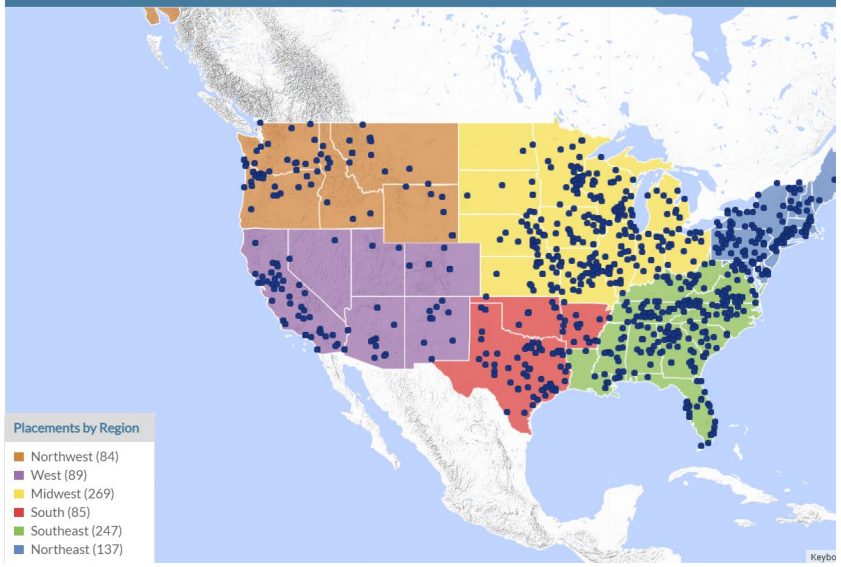
Word Count:
621

Print Downloads:
11

Site Audience	Placements	ROI
158,844,130	911	48 to 1
Desktop: 38,209,943 Mobile: 120,634,187	Online: 911 Print: 0	Total Ad Value: $410,694.00 Article Cost: $8,470.00

Retained Brand Mention
100%

Geographic Distribution



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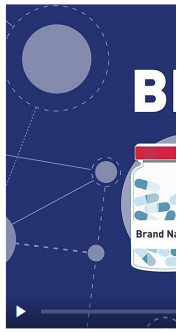

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(BPT) - If you have a chronic illness being treated by prescription medications, you probably already know your options for medications are sometimes limited — and how

Final Thoughts

- Medicines only work if patients have access.
- The generic and biosimilar industries have made outstanding contributions to public health by increasing access.
- 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!

And to the

The talented staff in the

Office of Therapeutic Biologics and Biosimilars

Office of Generic Drugs

Office of Pharmaceutical Quality


FDA
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ADMINISTRATION