U.S. FOOD & DRUG ADMINISTRATION

# User Fee Impact on FDA Programs

## FDA Small Business Regulatory Education for Industry Annual Conference
## REdI 2023 Plenary

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# User Fee Impact on CDRH Programs

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# MDUFA Program History

**MDUFA I - MDUFMA (FY2003-FY2007)**

Authorized FDA to collect user fees for the review of premarket submissions. Enacted to provide additional resources to an under resourced medical device program.

**MDUFA II - FDA Ammendments Act (FY2008-FY2012)**

Reauthorized user fee collections and established tiered performance goals for 510(k) and PMA.

**MDUFA III - FDASIA (FY2013-FY2017)**

Reauthorized user fee collections and increased resources for medical device programs. Created more aggressive performance goals and introduced interim performance milestones (RTA, SI).

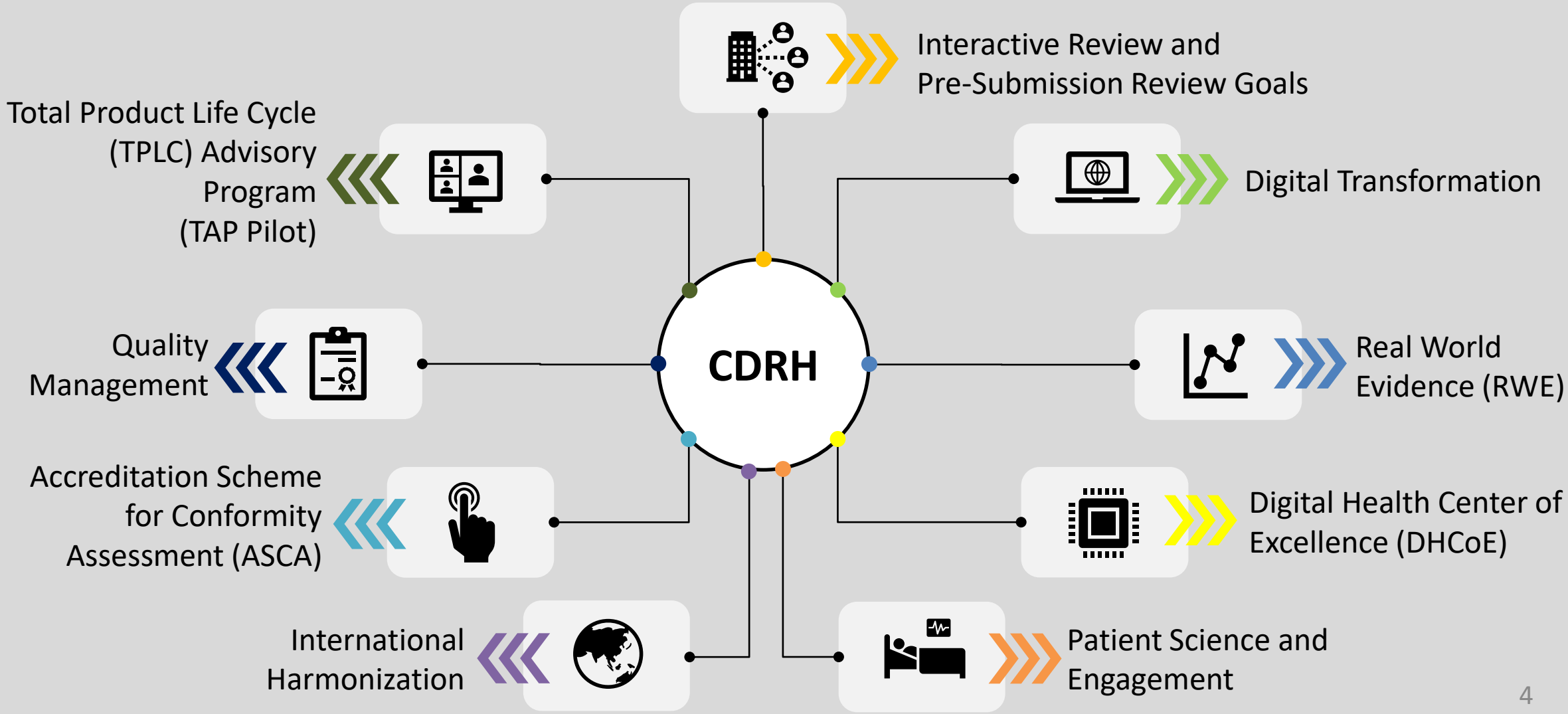
**MDUFA IV - FDARA (FY2018-FY2022)**

Reauthorized user fee collections, increased resources, created more aggressive performance goals for 510(k) and PMA, introduced new performance goals for De Novo and Pre-Sub. Support for NEST, digital health, ASCA Pilot, and patient engagement.

**MDUFA V - FDASLA (FY2023-FY2027)**

Reauthorizes user fee collections, increases resources, improves goals for PMA and 510(k) Total Time to Decision, Pre-Sub and De Novo, introduces new goal structure with “add-on” payments, support global harmonization, creates TAP Pilot.

# MDUFA V Supported Programs



# Enhanced Use of Consensus Standards:

## Accreditation Scheme for Conformity Assessment (ASCA)

## MDUFA V Commitments

- MDUFA IV pilot program intended to streamline conformity assessment aspects of device review and improve quality of testing
- Will transition from a pilot to a permanent program during MDUFA V
- Work with stakeholders to identify program enhancements and expansion criteria
- Provide training to FDA staff, industry, accreditation bodies and testing labs
- Track and report performance measures

# International Harmonization MDUFA V Commitments

- Expand engagement in international harmonization and convergence efforts
- Create a mechanism for working with regulatory partners with whom we have confidentiality commitments
- Assess extent of CDRH implementation of IMDRF technical documents
- Support creation of a forum to identify opportunities for regulators to leverage one another's approaches to decision making
- Participate in outreach activities to other regulators that encourage harmonization
- Issue a draft strategic plan in FY23, begin annual assessments in FY24

# Patient Science and Engagement Program in CDRH

## Voice of Patients

# CDRH's Journey Incorporating Patient Perspectives

**Patient Preference Initiative**

(2012)

**Partner with Patients Strategic Priority**

(2016-17)

**Patient Science and Engagement (PSE) Program**

MDUFA IV

(FY18-22)

**PSE Expansion and Integration**

MDUFA V

(FY23-27)

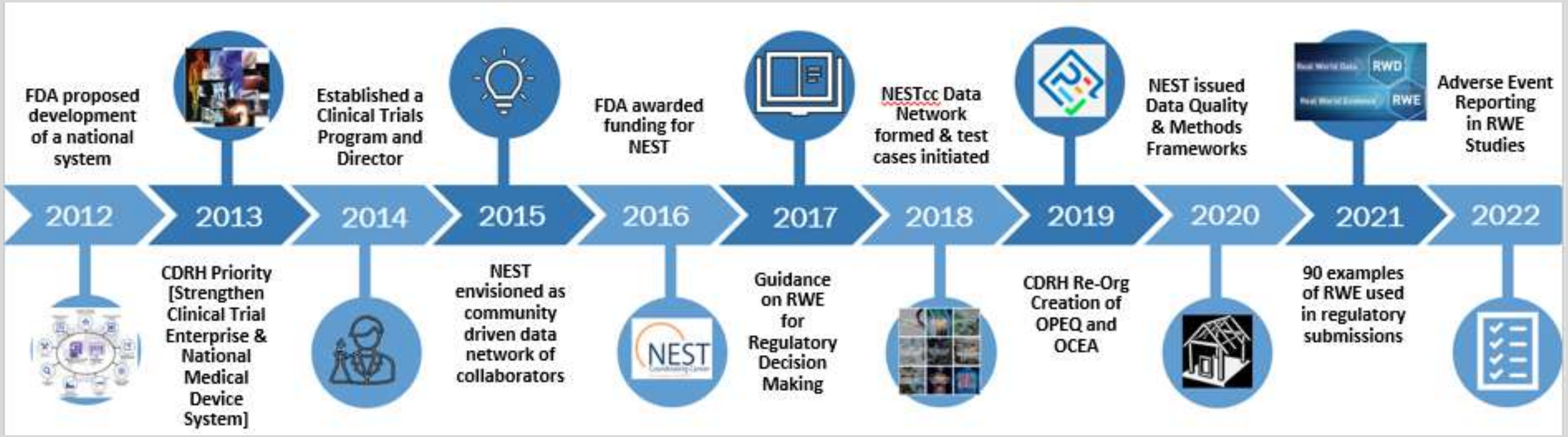
# Patient Science and Engagement MDUFA V Commitments

- Facilitate patient engagement through patient-friendly educational content
- Explore ways to advance health equity by incorporating data and perspectives from diverse patients
- Expand patient science review expertise and capacity
- Improve regulatory predictability and impact of patient science, including new research case examples
- Hold public meeting on patient-generated health data (PGHD) for collecting clinical outcome assessment (COA) data and for remote clinical trials
- Issue guidance on incorporating COAs into premarket studies and update patient preference information (PPI) guidance

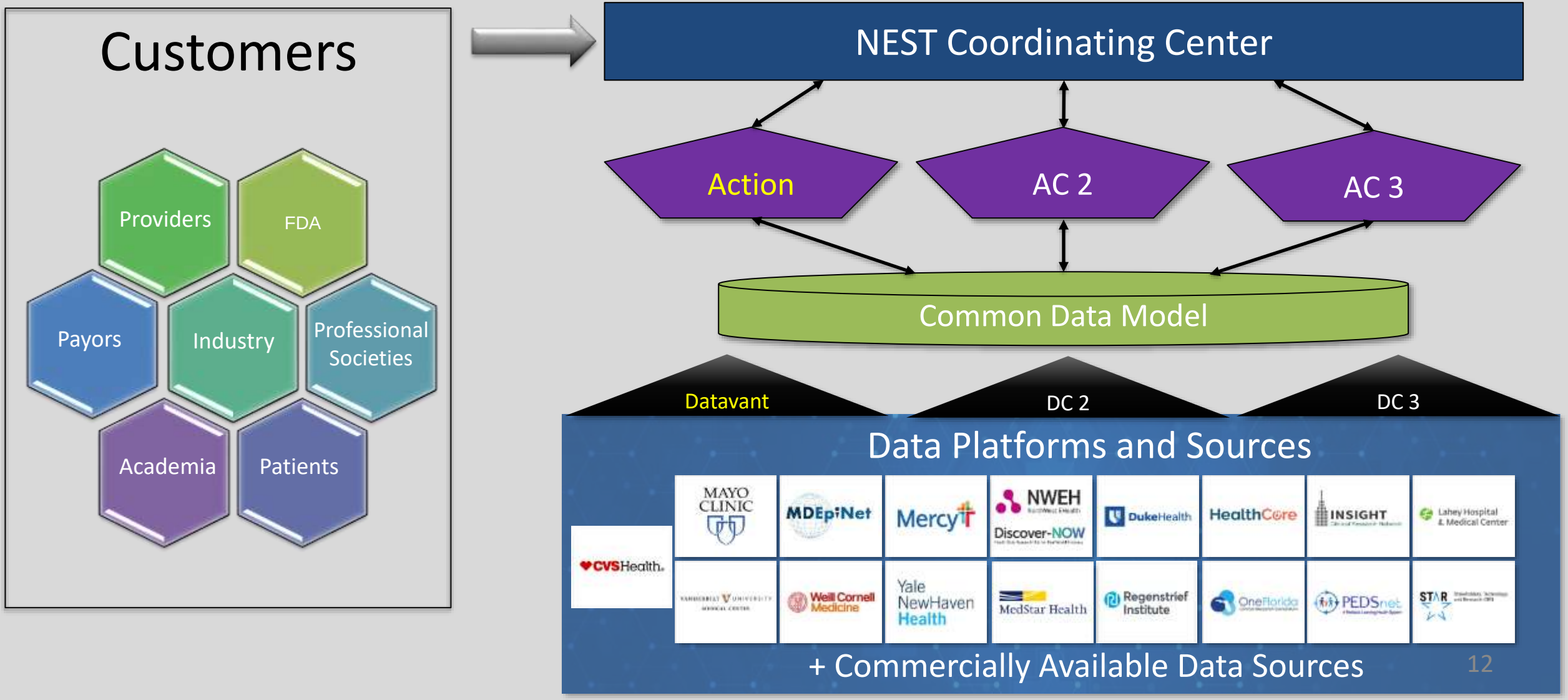
# Real-World Evidence (RWE) Program in CDRH

## Assess Technology When Used in Clinical Practice

# RWE: 2012 to Current State



# NEST - Infrastructure



# Real World Evidence MDUFA V Commitments

- Expand or develop RWE methods and policies for premarket submissions
- Update 2017 RWE Guidance
- Continue RWE training of review staff
- Transparent program updates, user-fee accounting
- Option for continued support for the National Evaluation System for Health Technology (NEST)

# Digital Health Program in CDRH

## Advance Innovation

# CDRH's Digital Health Journey

In early days of digital health, CDRH developed changes to its approach to and policy for digital health, and we built on that over time.

### Mobile Medical Applications

The Mobile Medical Applications guidance clarified that **FDA did not intend to regulate every health-related app**, and take **a platform-independent approach.**

2013

### 21st Century Cures Act

The 21st Century Cures Act **took our approach to digital health and built much of it into law**.

2016

### MDUFA IV

MDUFA IV helped us expand our Digital Health capabilities and supported the creation of **CDRH's Digital Health Center of Excellence**.

2017-2022

### Digital Health Precertification Pilot

Through the "Pre-Cert" Pilot Program, we explored innovative **tailored total product lifecycle approaches** to medical device software.

2017-2022

### Final Guidance Implementing "Cures"

Several guidance documents were updated or newly published as final to further implement the Cures Act, including the **function based approach.**

2019-2022

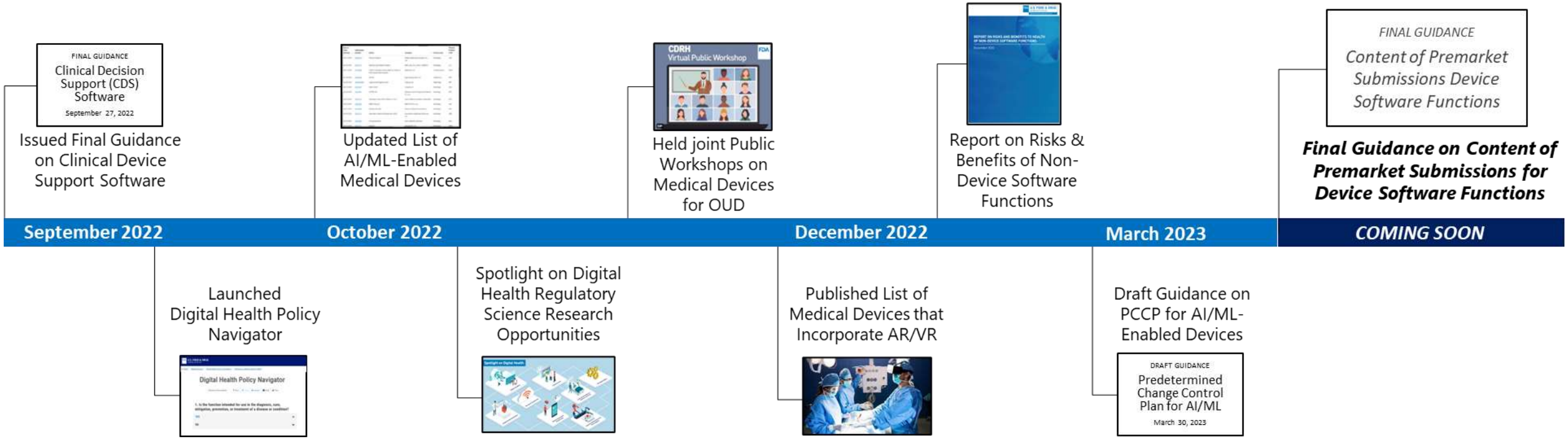
### AI/ML Initiatives

We led stakeholder engagement, shared a discussion paper, and an **AI/ML action plan** to further a total product lifecycle regulatory framework.

2019+

# CDRH's Digital Health Center of Excellence

continues momentum in digital health to support FDA's public health mission.



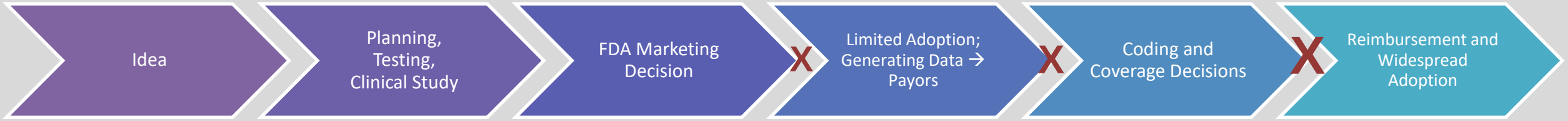
# Digital Health
# MDUFA V Commitments

- Build software and digital health technical expertise
- Streamline and align review with software lifecycles
- Participate in international harmonization and convergence
- Finalize guidance for device software functions
- Publish draft guidance on evaluating change control plans

# Total Product Lifecycle Advisory Program (TAP)

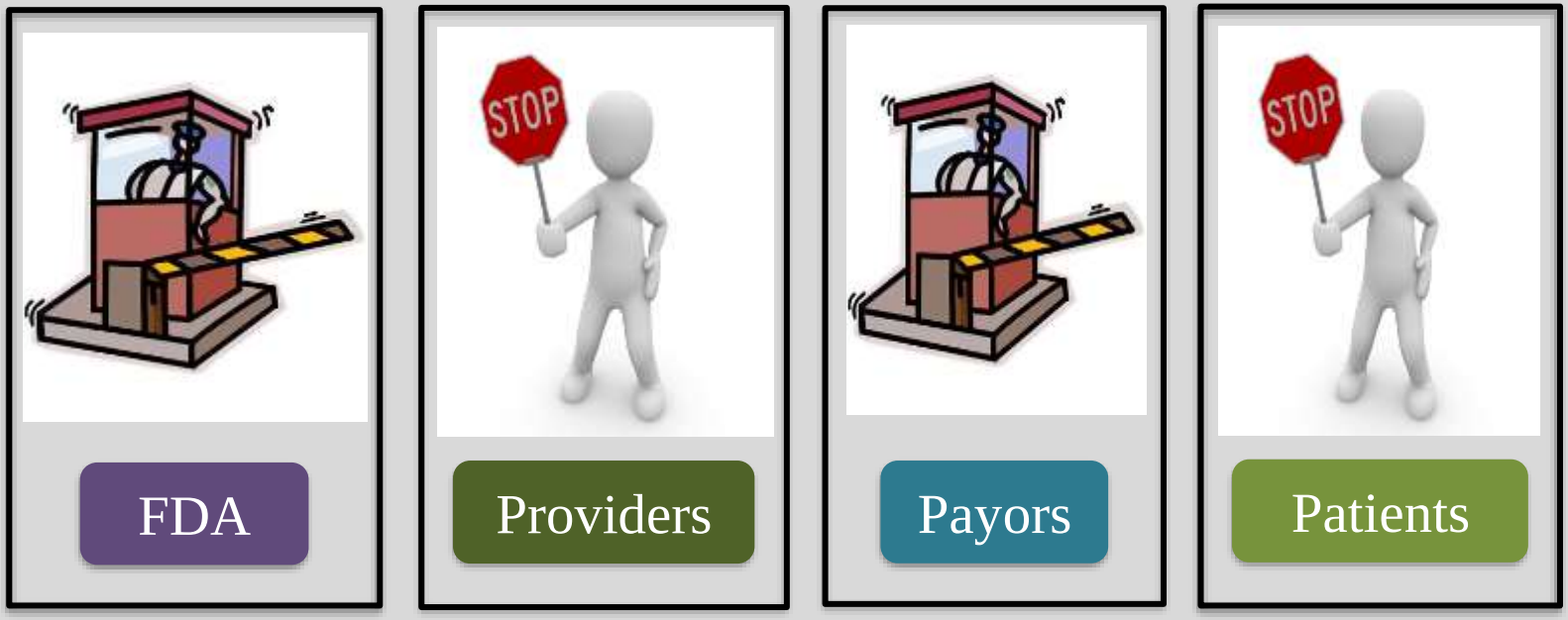
## Engagement with Device Developers

# Limits of Current Developer Engagement Opportunities




→ No single stakeholder has ownership of total process

→ It's not laying blame; it's just the way the system evolved

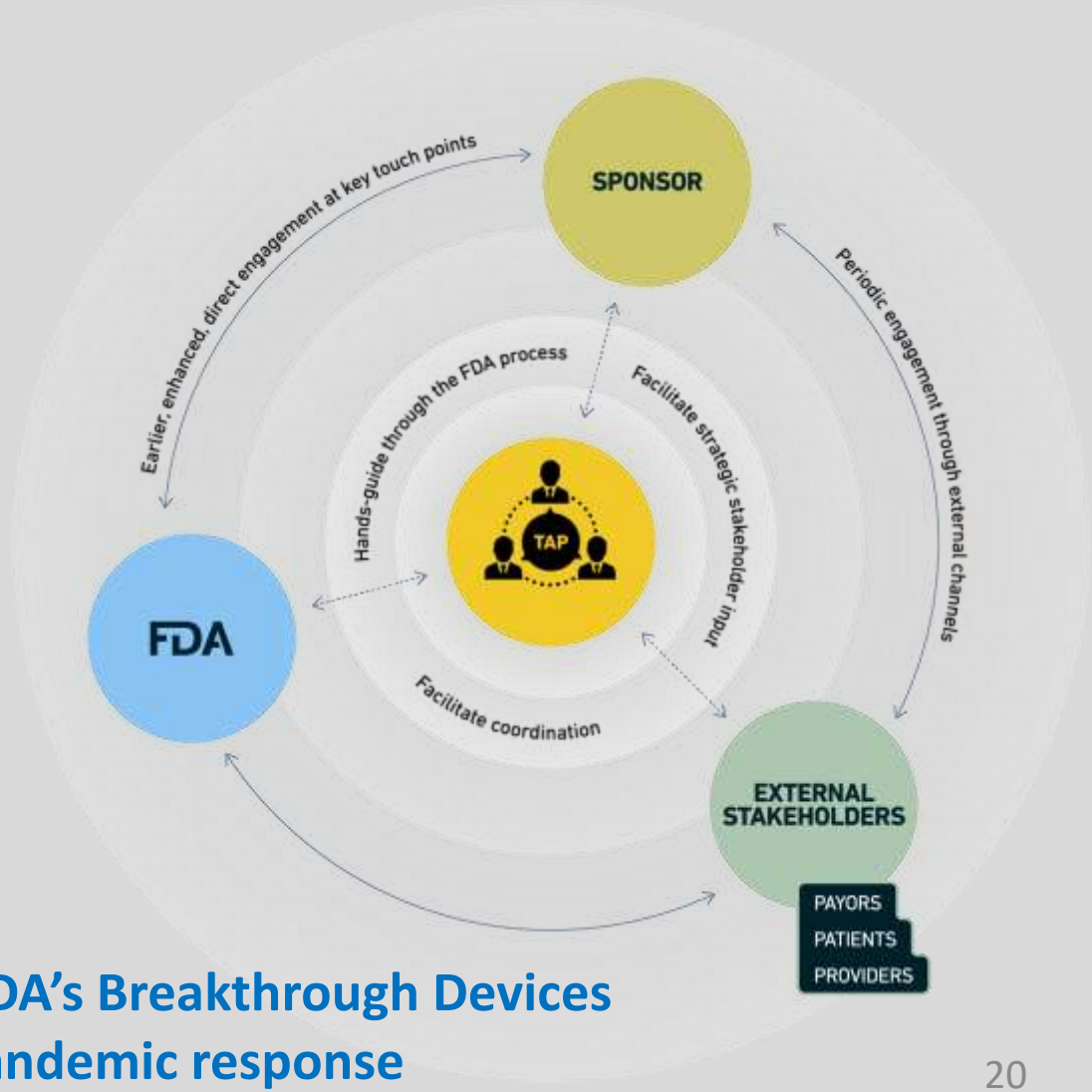


# TAP Pilot

**Long-term Vision |** Help spur more rapid development and more rapid and widespread patient access to safe, effective, high-quality medical devices of public health importance.

**Voluntary Pilot in MDUFA V**

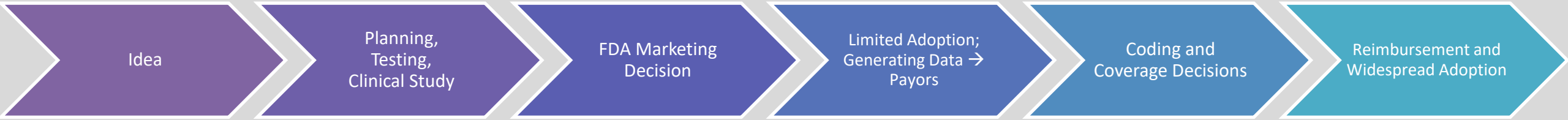
- Provide earlier and more frequent interactions with FDA, as well as facilitate coordination of earlier and more strategic stakeholder input, with a focus on Breakthrough and STeP devices.
- Begin with "soft launch" of up to 15 products in one CDRH OHT in FY 2023, and expand to enroll up to 325 products across multiple OHTs by end of MDUFA V.
- FDA will conduct an assessment of the TAP Pilot using an independent third party and include a participant survey and quantitative and qualitative success metrics.



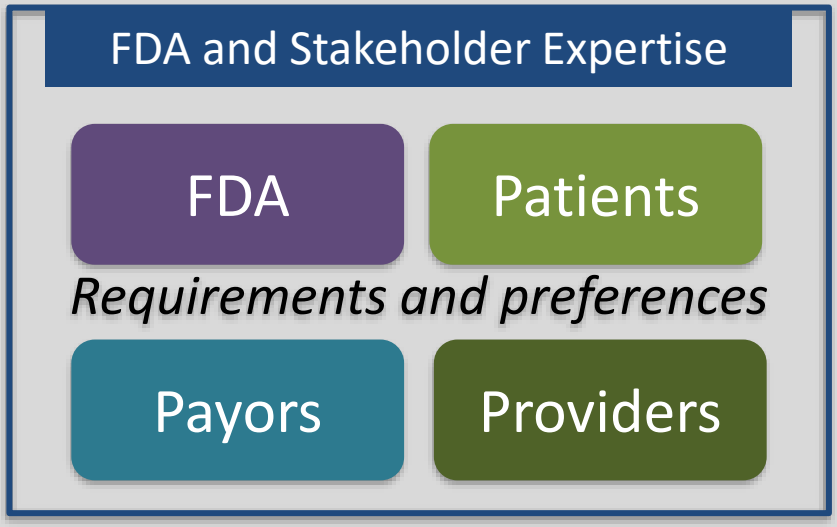

**Build upon lessons learned from FDA's Breakthrough Devices Program and COVID-19 pandemic response**

# TAP Pilot: Intended Impact

A shorter, happier journey




Many touch points early on




**Better evidence strategy for faster commercialization**

**Patient access**
**to high quality, innovative, safe, and effective medical devices**

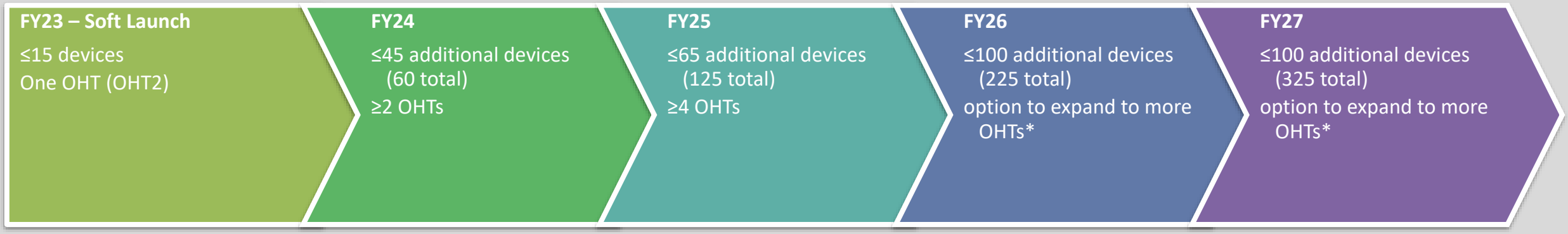
# TAP Pilot

## Implementation

- Starting w/OHT-2 (Cardiovascular)
- 15 companies with new Breakthrough Designation
- Teleconference within 14 days (90%)
- Biocompatibility/Sterility written feedback within 21 days (90%)
- Written feedback for other requests within 40 days (90%)

## Assessment

- Independent third party
- Quantitative metrics
  - Time from BDD/STeP to Marketing Submission
  - Time from Submission to Marketing Authorization
  - Requests for additional info during review
- Company satisfaction of interactions w/FDA and non-FDA Stakeholders



# Acronym Glossary

| | | | |
|---|---|---|---|
| **AI/ML** | Artificial Intelligence/Machine Learning | **OCEA** | Office of Clinical Evidence and Analysis |
| **ASCA** | Accreditation Scheme for Conformity Assessment | **OHT** | Office of Health Technology |
| **BDD** | Breakthrough Device Designation | **OPEQ** | Office of Product Evaluation and Quality |
| **COA** | Clinical Outcome Assessment | **OUD** | Opioid Use Disorder |
| **DHCoE** | Digital Health Center of Excellence | **PCCP** | Predetermined Change Control Plan |
| **FDARA** | Food and Drug Administration Reauthorization Act | **PGHD** | Patient-Generated Health Data |
| **FDASIA** | Food and Drug Administration Safety and Innovation Act | **PMA** | Premarket Approval |
| **FDASLA** | Food and Drug Administration Safety and Landmark Advancements Act | **PPI** | Patient Preference Information |
| **FY** | Fiscal Year | **PSE** | Patient Science and Engagement |
| **IMDRF** | International Medical Device Regulators Forum | **RTA** | Refuse to Accept |
| **MDUFA** | Medical Device User Fee Amendment | **RWE** | Real-World Evidence |
| **MDUFMA** | Medical Device User Fee and Modernization Act | **SI** | Substantive Interaction |
| **NEST** | National Evaluation System for health Technology | **STeP** | Safer Technologies Program |
| **NESTcc** | National Evaluation System for health Technology Coordinating Center | **TAP** | Total Product Lifecycle Advisory Program |

# Summary from CDRH

Lessons learned from previous cycles have informed the size and scope of today's MDUFA program

User fees collected as part of the MDUFA V legislation will allow us to meet the needs of our customers while driving innovation

# User Fee Impact on CDER Programs

**Patrizia Cavazzoni, MD**
Director
Center for Drug Evaluation and Research (CDER)
U.S. Food and Drug Administration

# User Fee Amendments (UFAs): Then and Now

- Timely review of applications is central to FDA's mission
- UFAs are essential to these efforts
- Before PDUFA's enactment in 1992, Agency lacked sufficient staff to perform timely reviews or develop procedures and standards to ensure a consistent and predictable premarket review process

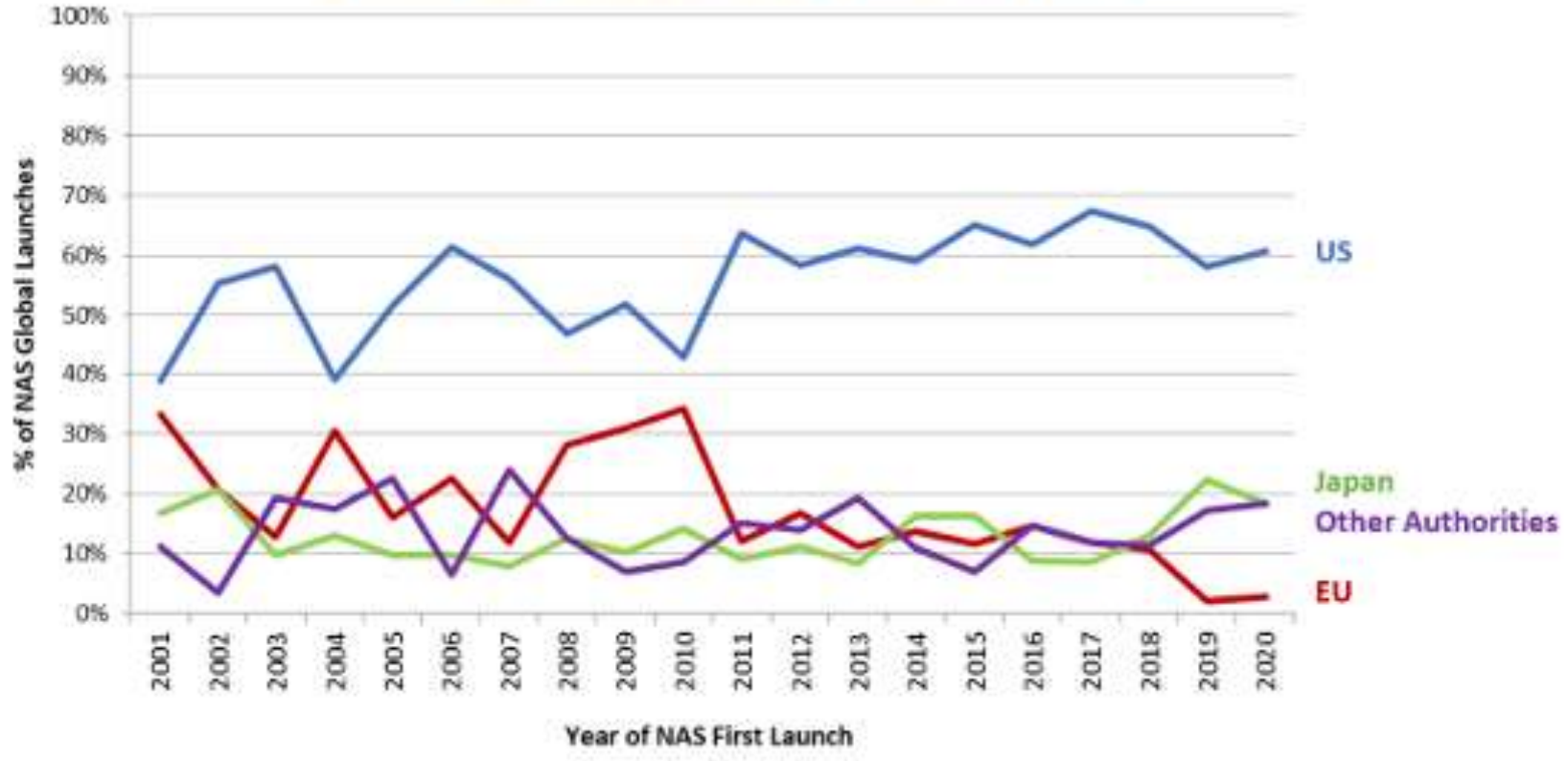
→ Americans' access to innovative, new medicines often lagged behind other countries

**PDUFA = Prescription Drug User Fee Amendments**

# User Fee Amendments (UFAs): Then and Now

- UFAs have enabled Agency to speed application review process
  - without compromising FDA's high standards for new drug safety, efficacy, and quality
- 5-year reauthorization cycles support continuous program innovation, evaluation, and improvement
- Enhancements improve potential for first-cycle approval, getting safe and effective drugs to patients sooner
- With these enhancements, the United States continues to be a global leader in drug innovation and Americans are now typically the first to benefit from new safe and effective medicines

# U.S. Share of New Active Substances (NAS) Launched on World Market, by region




Source: Scrip Magazine (2001 - 2005), PharmaProjects/Citeline Pharma R&D Annual Review (2007 - 2020)

* *New active substances (NASs): new chemical or biological entities where the active ingredient had received no prior approval for human use.*

# PDUFA VII

## Prescription Drug User Fee Amendments

# PDUFA VII Highlights

- **CBER |** Enhancing CBER's capacity to guide development and review innovative products such as Cell and Gene Therapies
- **Pre-Market |** Introducing new approaches to improve efficiency and expand communication in the human drugs review program
- **Regulatory Decision Tools |** Continuing application of innovative methods and tools to enhance regulatory decision-making
- **Manufacturing |** Facilitating manufacturing readiness and use of innovative manufacturing technologies

# PDUFA VII Highlights

- **Post-Market |** Ensuring safe use of medicines through continued enhancements to our drug safety system
- **Digital Health and Informatics |** Utilizing modern technology and supporting bioinformatics to enhance and streamline drug development and review
- **Finance |** Enhancing financial management and transparency
- **Hiring and Retention |** Focusing on strategic hiring and retention of world-class technical and scientific staff

# Rare Disease Endpoint Advancement (RDEA) Pilot Program

**Commitment under PDUFA VII:**

- Seek to advance rare disease drug development programs by providing a mechanism for sponsors to collaborate with FDA throughout efficacy endpoint development process
- Promote innovation and evolving science by sharing learnings on novel endpoint development through FDA presentations, guidance documents, public workshops, and public-facing website
- Develop FDA staff capacity to enable and facilitate development and use of novel endpoints to evaluate efficacy of rare disease therapies


# Vision

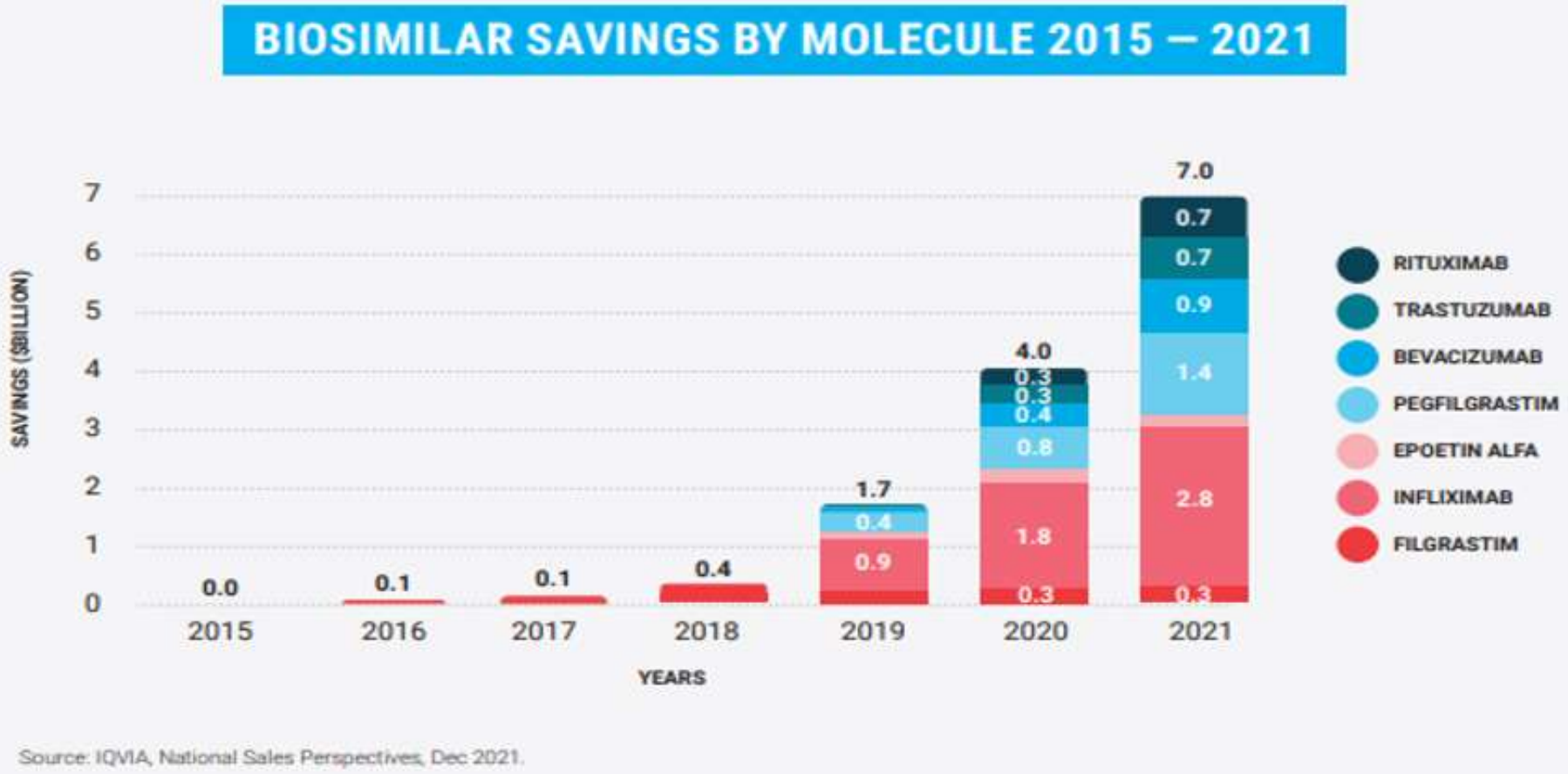
Speeding and increasing development of effective and safe treatment options addressing unmet needs of patients with rare diseases

# Mission

CDER's Accelerating Rare disease Cures (ARC) Program drives scientific and regulatory innovation and engagement to accelerate availability of treatments for patients with rare diseases

# Biosimilar Savings Totaled $7 Billion in 2021

## Since 2015, Biosimilars Have Generated $13.3 Billion in Savings




SOURCE: AAM / THE U.S. GENERIC & BIOSIMILAR MEDICINES SAVINGS REPORT 2022

# BsUFA III

## Biosimilar User Fee Amendments

# BsUFA III Highlights

- **Supplements |** Introducing new supplement types and expedited review timelines to expedite the review of supplements
  - Includes **faster review timelines** for safety labeling updates and labeling updates to add or remove an indication where FDA does not need to review efficacy data
- **Meeting Management |** Enhancing communication and feedback during biosimilar biological development process
- **Best Practices|** Implementing best practices in communication during application review

# BsUFA III Highlights

- **Inspections|** Enhancing pre-licensure inspection communication and clarifying use of alternative tools
- **Use-Related Risk Analysis (URRA) and Human Factors Timelines |** Introducing timelines for review of URRA and Human Factors studies
- **Interchangeable Products|** Introducing focused effort to advance the development of interchangeable products
- **Regulatory Science |** Introducing new pilot program to enhance regulatory decision-making and facilitate science-based recommendations

# BsUFA III Highlights

- **Finance |** Enhancing financial management and transparency
- **Hiring and Retention |** Focusing on the strategic hiring and retention of world-class technical and scientific staff
- **Information Technology|** Investing in modern technology to support enhanced and streamlined biosimilar product development and review

# BsUFA III – Regulatory Science

- Pilots a BsUFA regulatory science program broadly applicable to biosimilar and interchangeable biological product development
- Project goals should not be specific to a product or product class
- **Two demonstration projects**
  - Advancing Development of Interchangeable Products
  - Improving Efficiency of Biosimilar Product Development

# BsUFA III – Regulatory Science

- **Stakeholder engagement**
  - Public meeting on or before Oct 2025 to review progress and solicit input on future priorities
  - FDA will issue an interim report on project progress prior to meeting
  - Publish final summary report on pilot outcomes in FY2027

- **Deliverable**
  - Publish a comprehensive strategy document within 12 months of completing projects

# GDUFA III

## Generic Drug User Fee Amendments

# Generic Drugs and Patient Impact

**Generic drugs increase access**

More treatment **choices**

More **competition**

Lower **cost**

- In 2021, generic drugs generated **$365 billion** in savings
- Top three conditions that generated savings for patients by using generics instead of brand alternative are:
  1. Heart Disease: **$96.7** billion
  2. Mental Illness: **$59.7** billion
  3. Diabetes: **$56.7** billion
- Average copay:
  - **$56.12:** for brand-name drugs
  - **$6.61:** for generic drugs
- Generics represent only **3%** of total health care spending

Source: AAM U.S. Generic & Biosimilar Medicine Savings Report, 2022

# GDUFA III Highlights

- Minimizing issuance of complete response letters
  - Imminent actions
  - Extended goal dates
- Refined Pre-Facility Correspondence process
- Expanded Controlled Correspondence

# GDUFA III Highlights

- Expanded opportunities for early assessment of DMFs before certain priority ANDAs are submitted and between review cycles
- Continued enhancements to the regulatory science program and expedited complex generic drug development
- Goal dates for suitability petitions
- Enhancement of Management of User Fee Resources

**ANDA = Abbreviated New Drug Application**
**DMF = Drug Master File**

# GDUFA III:

## Advancing Earlier Cycle Approvals

### ANDA Communication and Review Enhancements

- **Reduced number of review cycles** through use of **imminent approval** and **goal date extensions** to resolve major or minor issues as appropriate

- **Revisions to Presubmission Facility Correspondence pathway** requirements

- Expansion of options for advice after complete response letter (CRL) by **adding to scope of controlled correspondence** and **post-CRL scientific conferences** in certain situations

# GDUFA III:

## Advancing Earlier Cycle Approvals

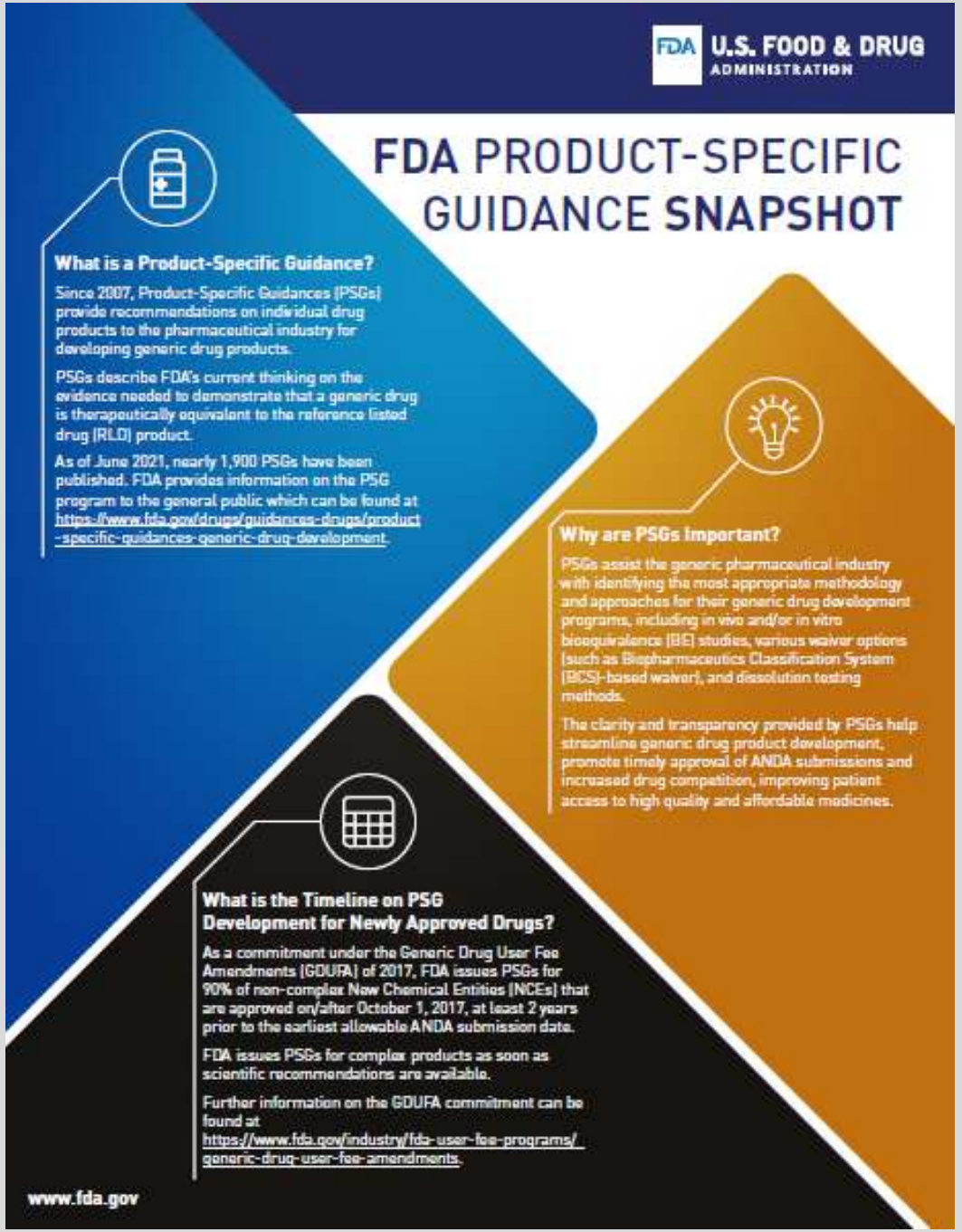
### ANDA Communication and Review Enhancements

- New goals around responses to **suitability petitions** to facilitate development of new ANDAs
  - Mechanism for prospective applicants to request permission to submit an ANDA that differs from reference listed drug (for example, different route of administration, strength, dosage form)

- Opportunities for teleconferences, correspondence and/or scientific meetings when there are **changes in product-specific guidances that impact ongoing bioequivalence studies**

# Product-Specific Guidances (PSGs)

- **257 PSGs in 2022**
  - **154 PSGs for complex products**, including
    - **54 new PSGs for complex products**
- **2000+** PSGs total



# GDUFA III:

## Enhancing Approval of Complex Generics

- **New goal for completion of PSGs for complex products**
- Establish new teleconference/meeting when PSG impacts ongoing bioequivalence studies

**Enhance Communications around Review**

- **Focus Pre-submission meetings** on key issues for review and assure review team participates
- Create option for more **enhanced scientific mid-cycle meeting** with goal of resolving more substantive issues within a single review cycle
- Establish **new post-CRL scientific meeting** to facilitate subsequent cycle approval

FDA Approves First Generic of Symbicort to Treat Asthma and COPD

FDA Approves First Generic of Restasis

# GDUFA Science and Research:

## Priority Initiatives for Fiscal Year 2023

1. Develop Methods for Generics to Address Impurities such as Nitrosamines
2. Enhance the Efficiency of BE Approaches for Complex Active Ingredients
3. Enhance the Efficiency of BE Approaches for Complex Routes of Delivery
4. Improve Efficiency of BE Approaches for Complex Dosage Forms and Formulations
5. Enhance the Efficiency of BE Approaches for Complex Drug-Device Combination Products
6. Improve the Efficiency of BE Approaches for Oral and Parenteral Generic Products
7. Facilitate the Utility of Model-Integrated Evidence (MIE) to Support Demonstrations of BE

**BE = bioequivalence**

www.fda.gov/media/162554/download

# Summary from CDER

- CDER's user fee support comes from PDUFA, BsUFA, GDUFA programs
- Efforts cascade throughout various CDER programs, including research efforts and collaboration with industry
- Programs advance FDA's role as global leaders in drug innovation, access and affordability

# User Fee Impact on CBER Programs

**Peter Marks, MD, PhD**
Director
Center for Biologics Evaluation and Research (CBER)
U.S. Food and Drug Administration

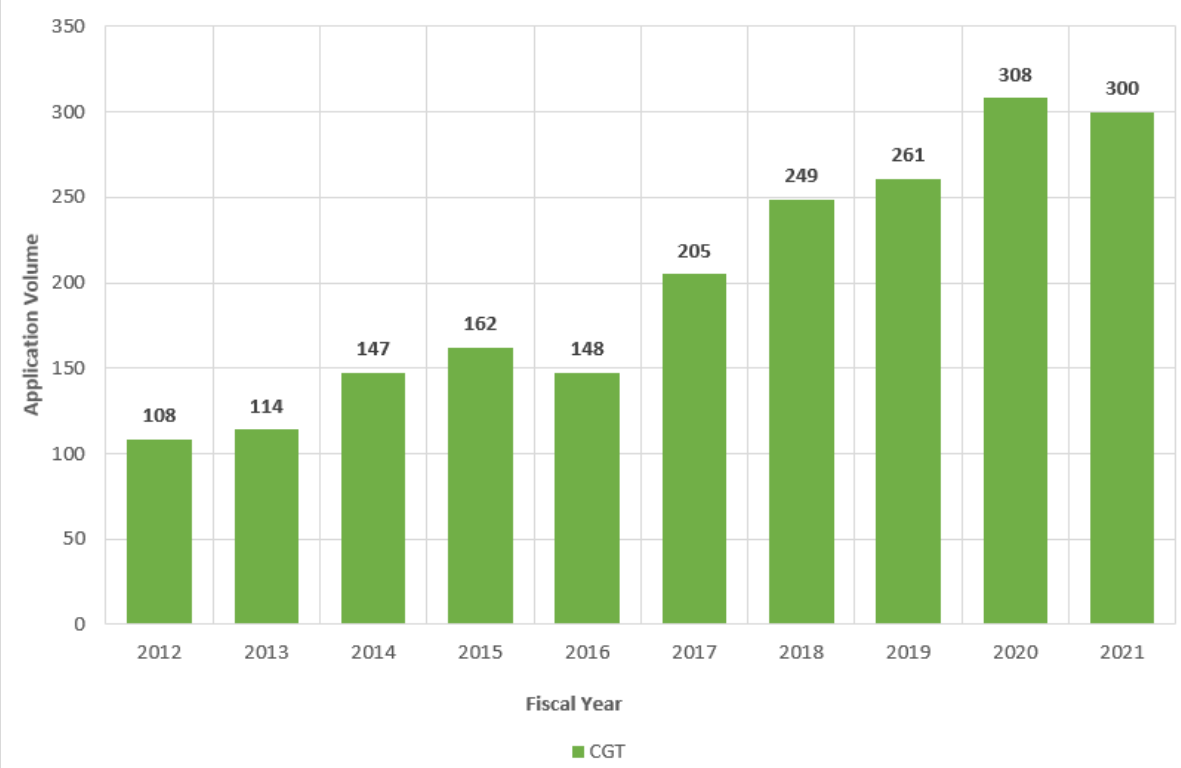
# CBER Products

# User Fee Programs at CBER

- PDUFA (≈92%)
- MDUFA (≈ 7%)
- BsUFA (<1%)
- GDUFA (<1%)

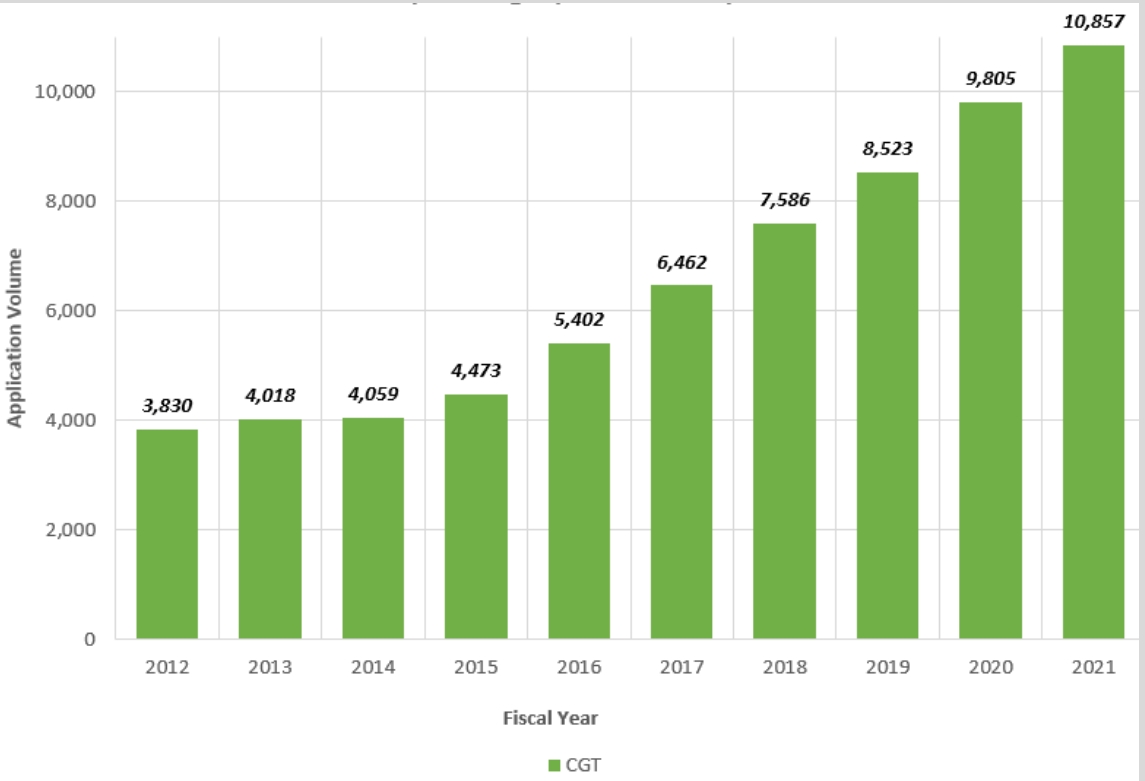
# Growth in Cell and Gene Therapy

Original Investigational New Drug Applications (INDs)




Excluding expanded access requests

IND Amendments




Including expanded access requests

# U.S. Approved Gene Therapies

- Kymriah (2017)
- Yescarta (2017)
- Luxturna (2017)
- Zolgensma (2019)
- Tecartus (2020)
- Breyanzi (2021)
- Abecma (2021)
- Carvykti (2022)
- Zynteglo (2022)
- Skysona (2022)
- Hemgenix (2022)
- Adstiladrin (2022)

# Selected PDUFA Commitment Areas

- Advanced Manufacturing
- Patient Focused Drug Development
- Reviewer Training
- Staffing

Additional directives as part of FDA Reform Act of 2022 (FDORA)

# PDUFA Commitment

## Cell and Gene Therapy (CGT) Targeted Hiring

- 125 FTE over next years
  - 100 FTE in office handling cell and gene therapy
  - 25 FTE in support offices
- Appropriate training and mentoring will be critical
  - Systems in place to accomplish this

**FTE = Full Time Equivalent**

# Addressing Growth in CGT

- Office of Tissues and Advanced Therapies (OTAT) recently has been reorganized into Super Office of Therapeutic Products (OTP)
  - Increase interactions with various stakeholders
  - Improve timeliness of responses and meetings
  - Enhance consistency of response

# OTP Super Office Structure

Branch | Division | Office | Super Office

**Super Office of Therapeutic Products**

**Super Office Director**

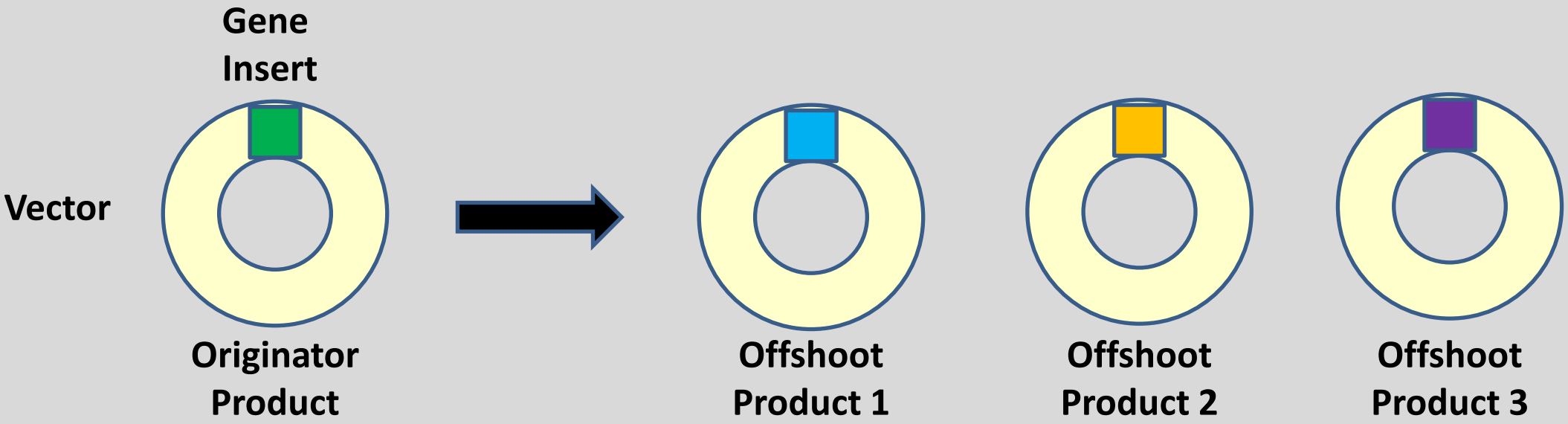
| Office of Gene Therapy CMC | Office of Cell therapy and Human Tissue CMC | Office of Plasma Proteins Therapeutics CMC | Office of Clinical Evaluation | | Office of Pharmacology Toxicology | Office of Review Management and Regulatory Review |
|---|---|---|---|---|---|---|
| **Gene Therapy I** | **Cell Therapy I** | **Hemostasis** | **General Medicine** | **Oncology** | **Pharm-Tox I** | **DRPM I** |
| Gene Therapy 1 | Cell Therapies 1 | Hemostasis 1 | General Medicine 1 | Oncology 1 | Pharm-Tox 1 | RPM 1 |
| Gene Therapy 2 | Cell Therapies 2 | Hemostasis 2 | General Medicine 2 | Oncology 2 | Pharm-Tox 3 | RPM 3 |
| Gene Therapy 3 | Cellular & Tissue Therapy | **Plasma Derivatives** | General Medicine 3 | | **Pharm-Tox II** | **DRPM II** |
| **Gene Therapy II** | **Cell Therapy II** | Plasma Derivatives 1 | General Medicine 4 | | Pharm-Tox 2 | RPM 2 |
| Gene Therapy 4 | Tissue Engineering 1 | Plasma Derivatives 2 | **Hematology** | | Pharm-Tox 4 | RPM 4 |
| Gene Therapy 5 | Tissue Engineering 2 | | Benign Hematology | | | |
| Gene Transfer Immunogenicity | Tumor Vaccine and Biotechnology | | Malignant Hematology | | | |
| | **Human Tissue** | | | | | |
| | Human Tissue/ Reproduction | | | | | |

**6 Offices**
14 Divisions
33 Branches

# Gene Therapy Initiatives

- Advancing manufacturing technologies for cell and gene therapy through research
- Work to more clearly define the use of accelerated approval for gene therapy
- Exploring concurrent submission and product review with other regulatory authorities
- Operation Warp Speed for Rare Diseases communication pilot

# Bespoke Therapeutics




## Premise

- In appropriate situations, non-clinical data and manufacturing information from one product may be able to be leveraged to another

# Leveraging Accelerated Approval

- The science inherent in the development of many gene therapies potentially facilitates the use of biomarkers as endpoints that are *reasonably likely* to predict clinical outcomes
  - Enzyme activity levels, structural protein levels can be measured and correlated with clinical endpoints in model systems or even in humans

# Global Cooperation

- Produce document on potential regulatory framework for cell and gene therapies for low- and middle-income countries (ongoing at WHO)
- Convergence of regulatory approach in high income countries (? harmonization in the future)
- Discussion of concurrent collaborative review process for gene therapy (Project ORBIS model)

WHO = World Health Organization

# Communications Pilot

## Operation Warp Speed for Rare Diseases

- **Background:**
  - experience with COVID-19 product development indicated potential benefits of frequent communication

- **Purpose:**
  - further accelerate pace of development of therapeutics for small populations with high medical need

# Communications Pilot

## Operation Warp Speed for Rare Diseases

- **Products eligible:**
  - products for life-threating rare genetic diseases showing promising efficacy early in development

- **Procedures:**
  - initial meeting followed by ongoing informal interactions via email or live meetings on an as needed basis

# Summary from CBER

- User fees are providing critically needed resources for the review of innovated cell and gene therapy products
- Initiatives cross many different areas from manufacturing to patient focused development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