EVERYLIFE FOUNDATION FOR RARE DISEASES

National Academies of Sciences, Engineering, and Medicine

Evaluating the Safety and Efficacy of Drugs for Rare Diseases or Conditions in the United States and the European Union

Annie Kennedy
Chief of Policy, Advocacy & Patient Engagement

BIOCENTURY

ARTICLE | POLITICS, POLICY & LAW

FDA too inconsistent in rare disease reviews, legislators say

Congressional leaders call on FDA create a task force to improve clarity, consistency in rare

The congressional request points to a problem that goes well beyond rare disease therapies: inconsistent approaches across FDA to similar regulatory questions. "Across the agency there remains significant uneven application of rare disease policies, guidance, and expertise, even, at times, for the same product tated.

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POLITICOPRO

Experts fear FDA push to get neurological drugs to market faster shortchanges patients

By Katherine Ellen Foley

10/20/2023 05:00 AM EDT

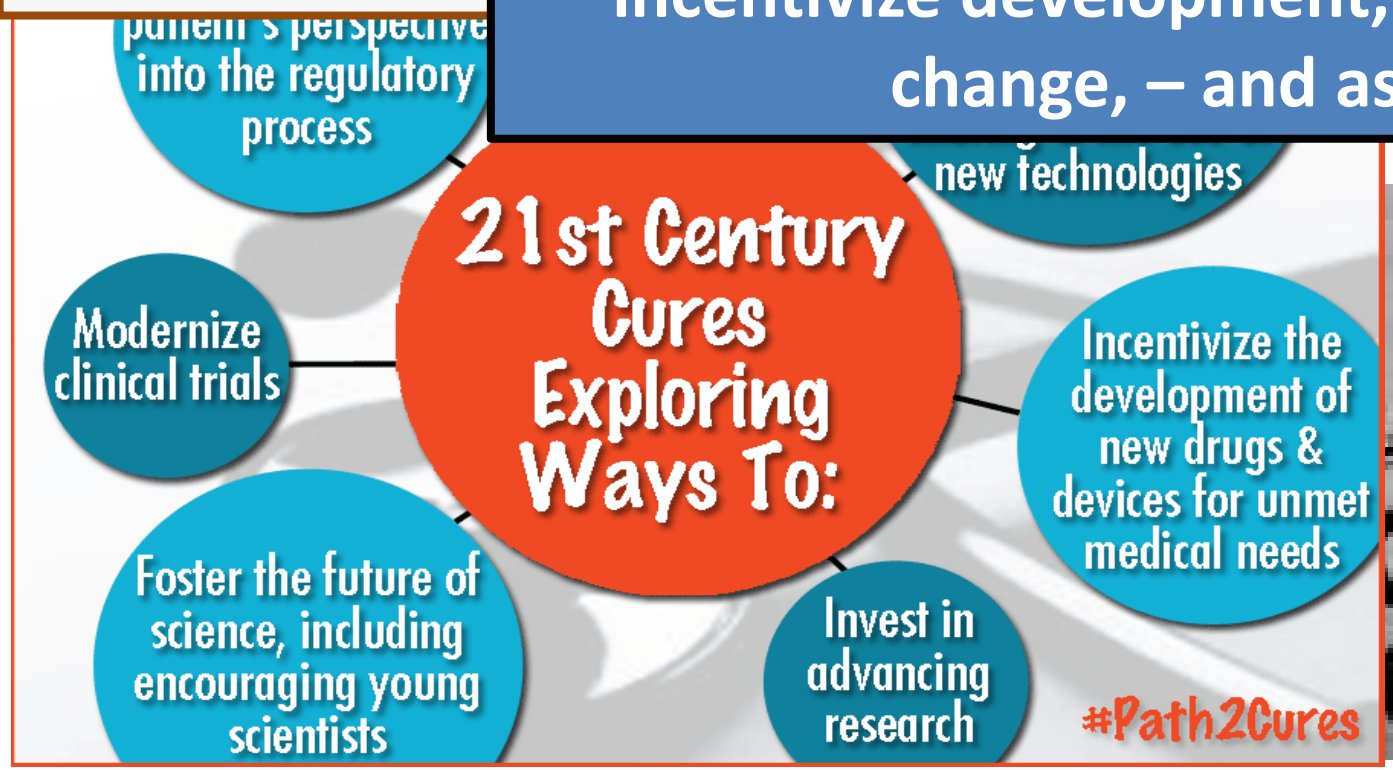
The push to bring new treatments sooner to patients instead.

ADVERTISEMENT

This New Treatment Could Save the Lives of Babies. But It Costs $2.1 Million.

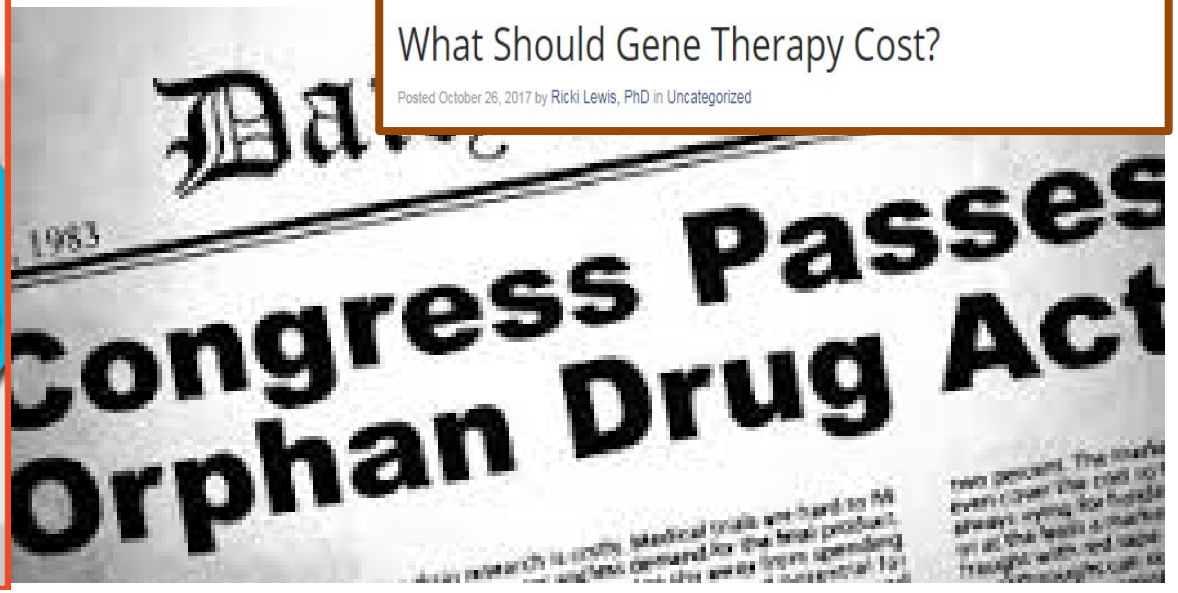
The price set by the Swiss drugmaker for a single treatment — prompting re pay for gene-therapy breakthroughs.

The U.S. healthcare system is grappling with how to incentivize development, measure meaningful change, – and assess value…



What Should Gene Therapy Cost?

Posted October 26, 2017 by Ricki Lewis, PhD in Uncategorized



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Signs of Progress….

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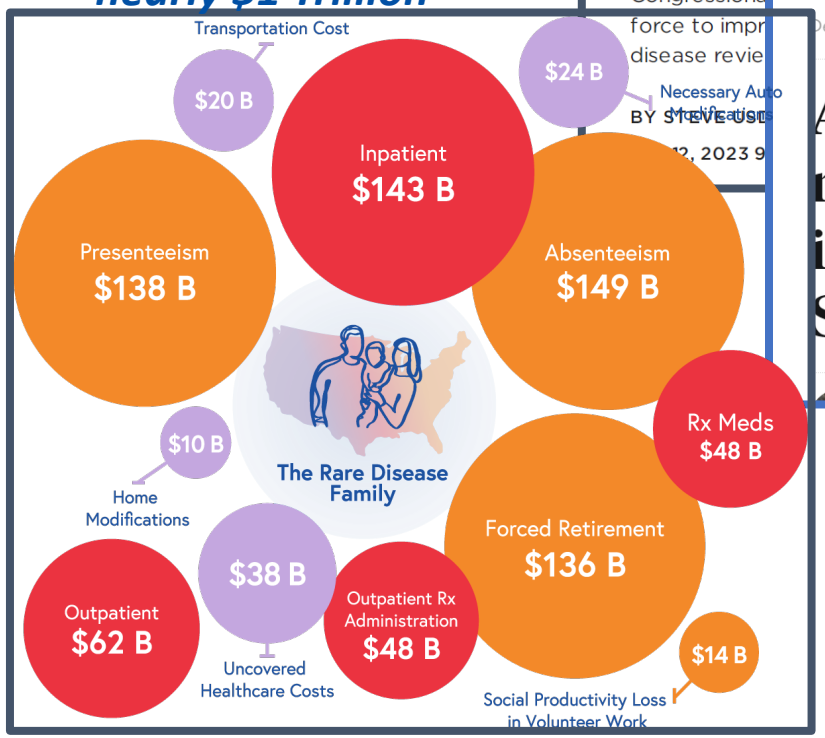
And Reason for Concern…

Conservative Estimate of Economic Impact in U.S. Based on 379 of 10,000 RDs in 2019 was nearly $1 Trillion



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BY STEVE USD
…2, 2023 9

December 3, 2021 07:16 AM EST *Updated 07:29 AM* | FDA+

Accelerated approval reforms nee meaningful confirmatory trial improvements, professors write i

| HEALTH OUTCOMES | CONTROLLED TRIALS | TECHNOLOGY | SYSTEMS OF CARE

Medicare's Aducanumab Decision Highlights Needed Reforms To FDA And CMS Regulatory Pathways

Sean R. Tunis, Pei-Jung Lin, James D. Chambers, Peter J. Neumann

EDT *Updated 11:55 AM* | People, R&D

…lays off 160+ staffers, winds down facility, punts clinical programs in drastic revamp

Amber Tong
Senior Editor

With respect to deployment of existing flexibilities by regulators when evaluating drugs for rare diseases - what is working well, and what could be enhanced?

What are barriers to patients benefitting from today's robust pipelines? What enhancements or incentives could serve as force-multipliers?

How are patient community expertise and patient experience data (PED) being utilized especially related to developing outcome measures, new clinical programs, and informing regulatory decisions?

Which members of our rare disease community have been/are being left behind? How can regulatory science support overcoming existing hurdles for those not yet experiencing progress?

Regulatory Flexibilities – Opportunities for Increased Predictability and Consistency

With respect to deployment of existing flexibilities by regulators when evaluating drugs for rare diseases - what is working well, and what could be enhanced?

What are barriers to patients benefitting from today's robust pipelines? What enhancements or incentives could serve as force-multipliers?

Regulatory Flexibilities – Opportunities for Increased Predictability and Consistency

In rare disease, natural history of a disease is - in and of itself - a threat.

Doing nothing = Doing harm

Improvement = slowed or stopped disease progression

Rare disease reality is that incremental advances are more likely than breakthroughs –

Thus, we must take ALL steps forward – and then build on them

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LACK OF CLARITY

around regulator expectations discourages companies from investing in complex but high-need populations.

EXPANDED PARTNERSHIP

between FDA, professional societies, and disease experts is **NEEDED** to create consensus recommendations for biomarker acceptance

CONTINUED COMMUNICATION

between FDA, industry sponsors, and patient communities is needed post-approval throughout the confirmatory trial phase

DE-RISKING DRUG DEVELOPMENT

for rare indications requires consistency across applications

ACCELERATED APPROVAL MAY BE THE ONLY PATH FORWARD FOR MANY RARE DISEASES

POST-APPROVAL RANDOMIZED CONFIRMATORY TRIALS

pose ethical challenges when there is no longer clinical equipose

the absence of consistency leads to **AMBIGUITY, DELAYS** and **CONFUSION**

DRUG DEVELOPMENT

using biomarkers is **NOT** a **COMPROMISE**

SURROGATE ENDPOINTS

(biomarkers)

Can more accurately capture real-time disease progression or improvement

Well-established biomarkers have enabled

ACCELERATED APPROVAL

to transform oncology drug development

We must invest in

PRE-COMPETITIVE RESEARCH

to further characterize rare disease bio-markers

the sketch effect
VISUAL COMMUNICATION SOLUTIONS

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National Academies of Sciences, Engineering, and Medicine

Regulatory Pathways – Accelerated Approval

Strengths

- CBER eager to use the AA pathway for gene therapy
- AA is essential for slowly progressive rare diseases where it would take many years to measure clinical benefit
- Recent orphan designated approvals utilizing the AA pathway show primary disease activity biomarkers can be leveraged to support AA

Accelerated approval is NOT a lower standard. Treatments approved via the AA pathway are **subject to the same statutory standards** for proving safety and efficacy as traditional drug approvals.

Policies that regard treatments approved via the AA pathway as experimental **exacerbate health inequity** among communities eligible for potentially life-altering and lifesaving medications.

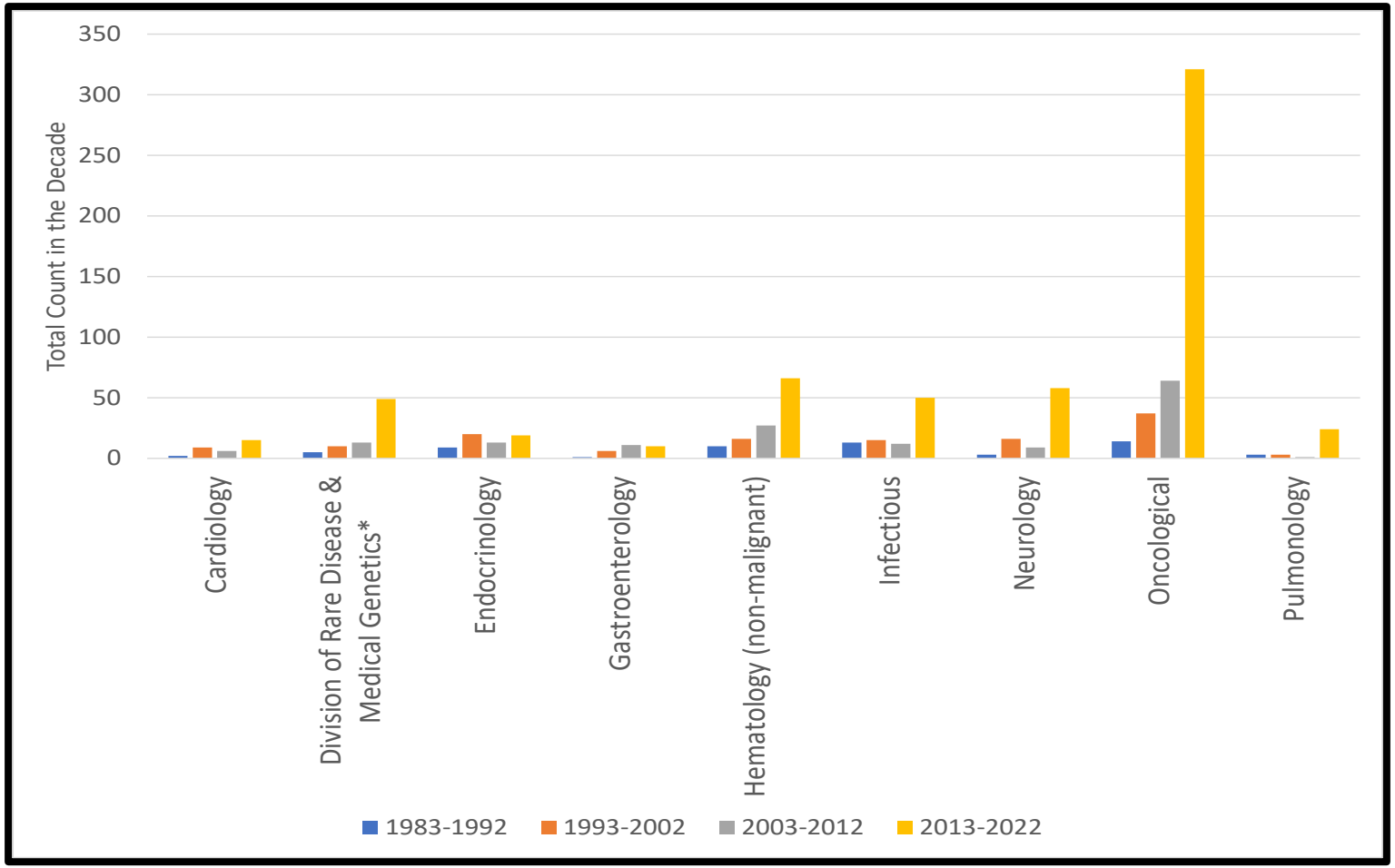
Challenges

- Limited well-characterized surrogate endpoints
- Inconsistent and shifting decisions over the appropriateness of AA across CDER
- Additional complexities inherent in rare disease confirmatory trial conduct (very small populations, ethical concerns, accounting for newly approved products during study conduct)
- Concerns regarding implementation of FDORA authority to require confirmatory trial enrollment prior to approval – especially in ultra-rare
- Access environment

Regulatory Flexibilities – Opportunities for Increased Predictability and Consistency

Orphan Drug Approvals by Disease Area for those with More Than 25 Orphan Drug Approvals

Ordered from Most Frequent in Total to Least



** this grouping of Rare Disease & Medical Genetics is done to be consistent with the FDA Divisions in 2022*

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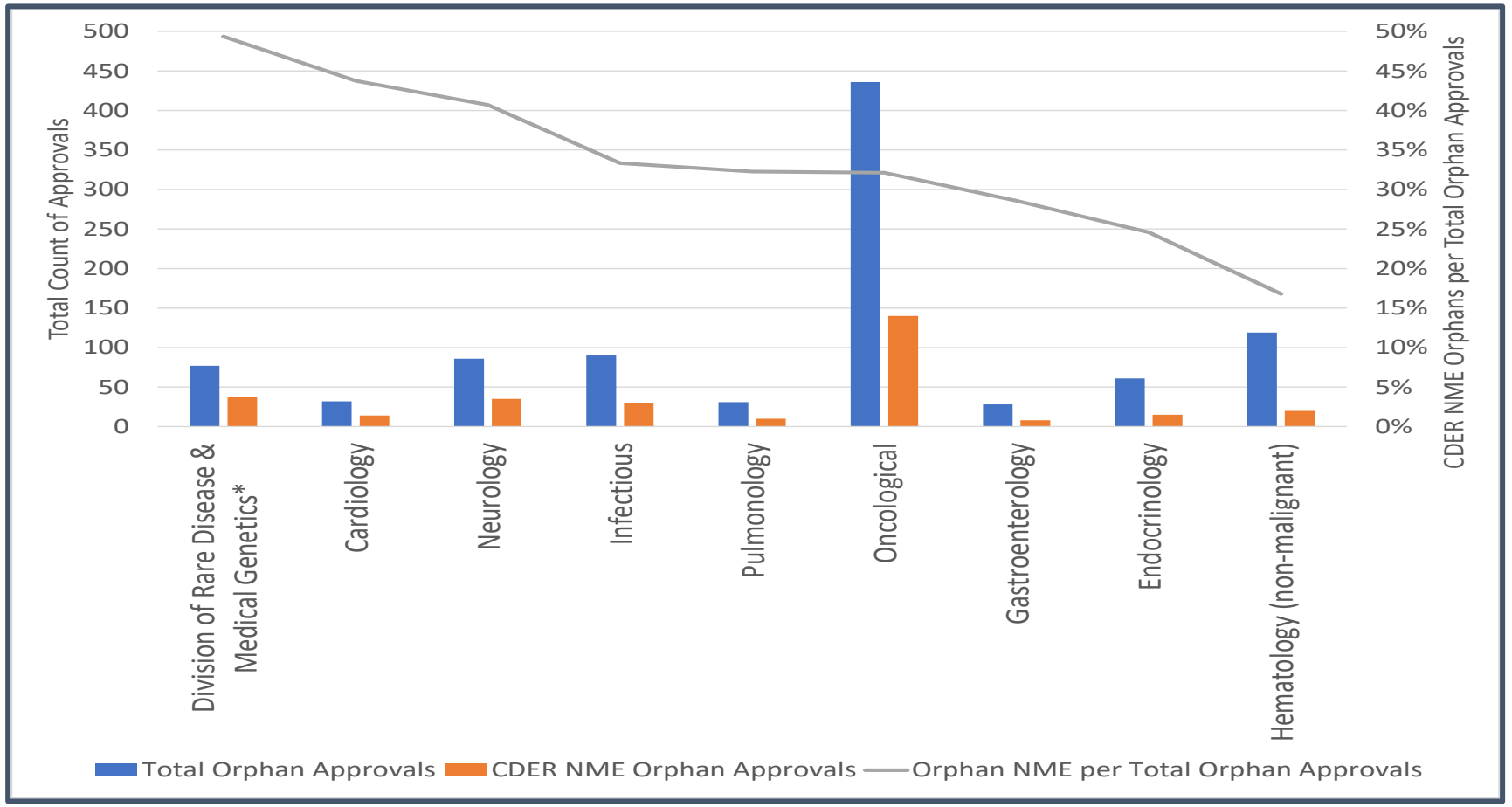
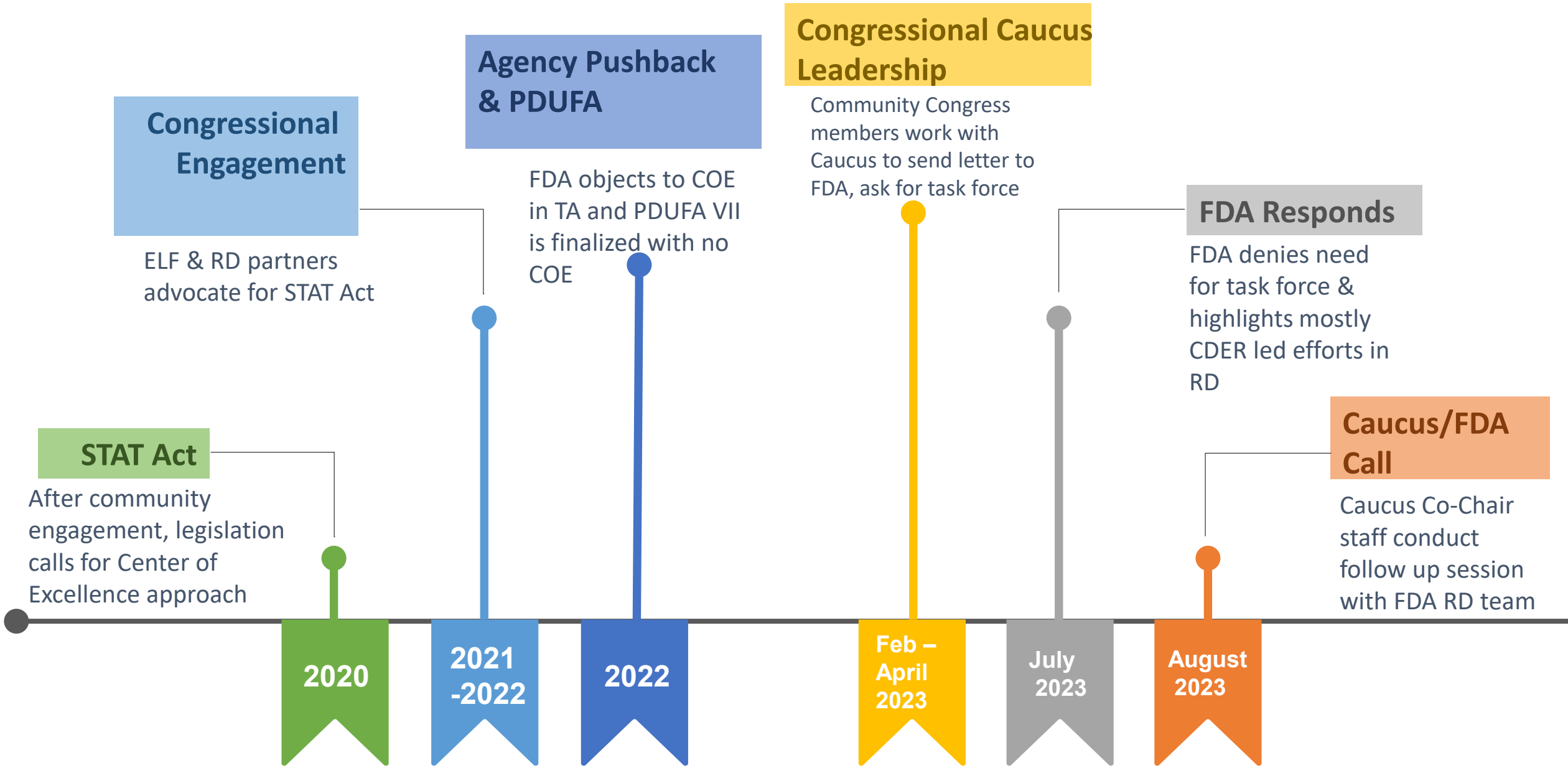
Count of Orphan Approvals by Disease Area
Segregated Based on NME Designation by CDER –
and Ordered from Most Frequent NME to Least
Progress is Uneven



this grouping of Rare Disease & Medical Genetics is done to be consistent with the FDA Divisions in 2022

Rare Disease Community Seeking More Consistency



Strengths:

- The agency is good at granting flexibility when:
  - there is good natural history data,
  - plausible mechanistic data, or
  - clinical data suggesting efficacy and a reasonable safety profile.

(Caveat -- However, we mainly see these flexibilities at the time of review/approval vs. being more thoughtful on flexible approaches during development.)

Regulatory Flexibilities – Opportunities for Increased Predictability and Consistency

Challenges:

- Need for more understanding of how much data is needed and when would benefit sponsor planning
- Need for additional resources for biomarker and surrogate endpoint development; earlier acceptance within program
- Greater consistency in applying existing flexibilities and pathways would also be very beneficial,
- Sponsors and PAGs often report a lack of transparency related to development interactions
  - sometimes results in months long delays in decision- making progress (especially with written response only comments);
  - notable differences in how different divisions operate with respect to communication practices

Regulatory Flexibilities – Opportunities for Increased Predictability and Consistency

"None of us are as smart as all of us."
Satchel Paige

Opportunities:

- Infrastructure for flexibility in the US is present but inconsistently applied (across FDA Divisions/Centers) & would benefit from regulators sharing learnings across therapy areas
  - Opportunity for the creation of a searchable database on regulatory decisions, associated endpoints, & how FDA utilizes patient reported outcomes in its benefit-risk assessments.
  - Expanded data sharing, assessments, and best practices in rare disease regulatory science should be actively encouraged/incentivized across all stakeholder communities
- More flexible approaches earlier in development programs would be particularly helpful for diseases where traditional approaches are highly difficult or outright impossible
- With newborn screening, opportunities to enroll pre-symptomatic patients
- Greater use of RWE and composite endpoints that are tailored to both the disease state and the patient at the time of dosing
- US & EU have a MOU for shared reviews and could leverage this more in rare disease considerations

Utilization of Patient Experience & Patient Experience Data (PED)

How are patient community expertise and patient experience data (PED) being utilized especially related to developing outcome measures, new clinical programs, and informing regulatory decisions?

Utilization of Patient Experience & Patient Experience Data (PED)

Strengths:

- FDA has a well established, formalized process of PFDD with various processes to share disease community insights & preferences:
  - PFDD workshops, Listening Sessions, Ad Comms Open Public Hearings, Voice of the Patient Reports, Formalization of the PED Checklist, etc
- Guidances encouraging inclusion of patient community engagement

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TABLE OF CONTENTS

8 FOCUS AREAS

BY THE NUMBERS

23 Leadership and Steering Committee Members

88 TOTAL Subject Matter Experts
- 8 Academia
- 40 Industry
- 28 Patient Advocacy Organizations
- 5 Payer Organizations
- 7 Other

20 FDA Guidances

12 Hours of Workshops

8 Cross-Cutting Topics and Sets of Action Steps

4 Workshop Summaries

112 Resources Linked in This Guide

Utilization of Patient Experience & Patient Experience Data (PED)

Challenges:

- Unclear how patient centric data / perspectives are utilized by review teams in regulatory decision-making, as many US & EU dossiers do not provide detailed information about patient data which were considered and/pr were relied upon in granting approvals or label citations. More transparency would benefit all.
- Many communities feel that PFDD workshops & VoP reports yield not change; insights/learnings not reflected in Guidances, clinical programs.
- Expert opinions not being fully utilized earlier in the review process; this is critical in rare disease

Opportunities:

- FDA should be applauded for their initial PFDD accomplishments, as well as provided additional resources and authorities to expand upon successes to date.
- Reviewer training on the role PED can and should play in decision-making
- Documentation not just of the patient experience data, but of how it informed their thinking and decision-making;
- PFDD Workshops should trigger meaningful momentum and thus be a part of a series of engagements between Agency, PAGs and relevant stakeholders – not a point in time event;
- Importance of using patient experience data to liberalize endpoints;
  - FDA develop more flexible *Guidance for Surrogate Endpoint Development (Biomarker and Intermediate Clinical Endpoints) with Expedited Implementation*?

Utilization of Patient Experience & Patient Experience Data (PED)

Opportunities:

- Enhance how we incorporate PED in pivotal programs;
- Expand use of objective PED; opportunity for patient preference studies?
- Opportunities to include PED in agency review of product labeling and part of risk-benefit analysis (ARC program)
- Opportunity for FDA/others to provide a critical assessment across programs as to what worked well and why – as well as capturing key performance aspects for broader internal dissemination/application

Which members of our rare disease community have been/are being left behind?

How can regulatory science support overcoming existing hurdles for those not yet experiencing progress?

- Most rare diseases affect fewer than 20,000 Americans -- or 10% of the 200,000 threshold.

- Global conversation –
  - European Medicines Agency (EMA) and several other health authorities informally consider a disease to be ultra rare if it effects less than 1 in 50,000
  - Many in the U.S. have established their own suggested thresholds between 2,000 and 20,000

- The common threads in these definitions are the lack of a scientifically backed justification for the chosen cutoff and trepidation to establish such a formal cutoff for fear of the potential repercussions.

Small Populations – Ultra Rare Disease

- Regardless of a new designation/ threshold –
- Since the passage of the Orphan Drug Act 40 years ago – the increasing momentum has yielded approvals for fewer than 5% of rare diseases –
- Only 37 rare diseases are on the Federal Recommended Newborn Screening Panel (thus less than a fraction of a percentage can be identified in the optimal therapeutic window)
- And federal rare disease funding and innovation incentives are eroding – not increasing

- Conditions with very small populations (ultra-rare) face increased difficulties with novel therapy development: hosting clinical trials due to low prevalence, unique regulatory, funding, and research hurdles

- May require tying such requests to a formal characterization or definition of “ultra rare”, guiding who becomes eligible for new programs or flexibilities.

- The EveryLife Foundation & rare disease community advocated for funding to allow the National Academy of Sciences to produce a report that would convene expert stakeholders to establish:
  - what data is needed to define ultra-rare,
  - which critical stakeholders are required for this determination,
  - where the data gaps for determining this definition are,
  - and to identify opportunities to define ultra-rare outside of population.

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Time is Our Most Precious Commodity


IPS HEART receives FDA Rare Pediatric Drug Desig
of its Stem Cell Drugs for Duchenne M
April 13, 2023 11:48 AM Eastern Da
X4 Pharmaceuticals Announces Submission of New Drug Appli
U.S. FDA for Mavorixafor in WHIM Syndrome
September 5, 2023
Submission supported by posi
FDA Accepts Application for Genentech's Crovalimab for the Treatment of PNH, a Rare Life-Threatening Blood Condition
Friday, September 8, 2023
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FDA and has
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We MUST progress forward
FDA Braces for Looming B
and Gene Therapy Submi
Published: Jun 12, 2023 | By Ana Mulero
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OATD-01 with U.S
Phase 2 pulmona
June 23, 2023 03:00 ET| Source:
Zevra Therapeutics Announces FDA Acceptance of IND Application for KP1077 in Narcolepsy
Published: May 03, 2023
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nnounces Plans to File IND Application in Neuropathic Pain
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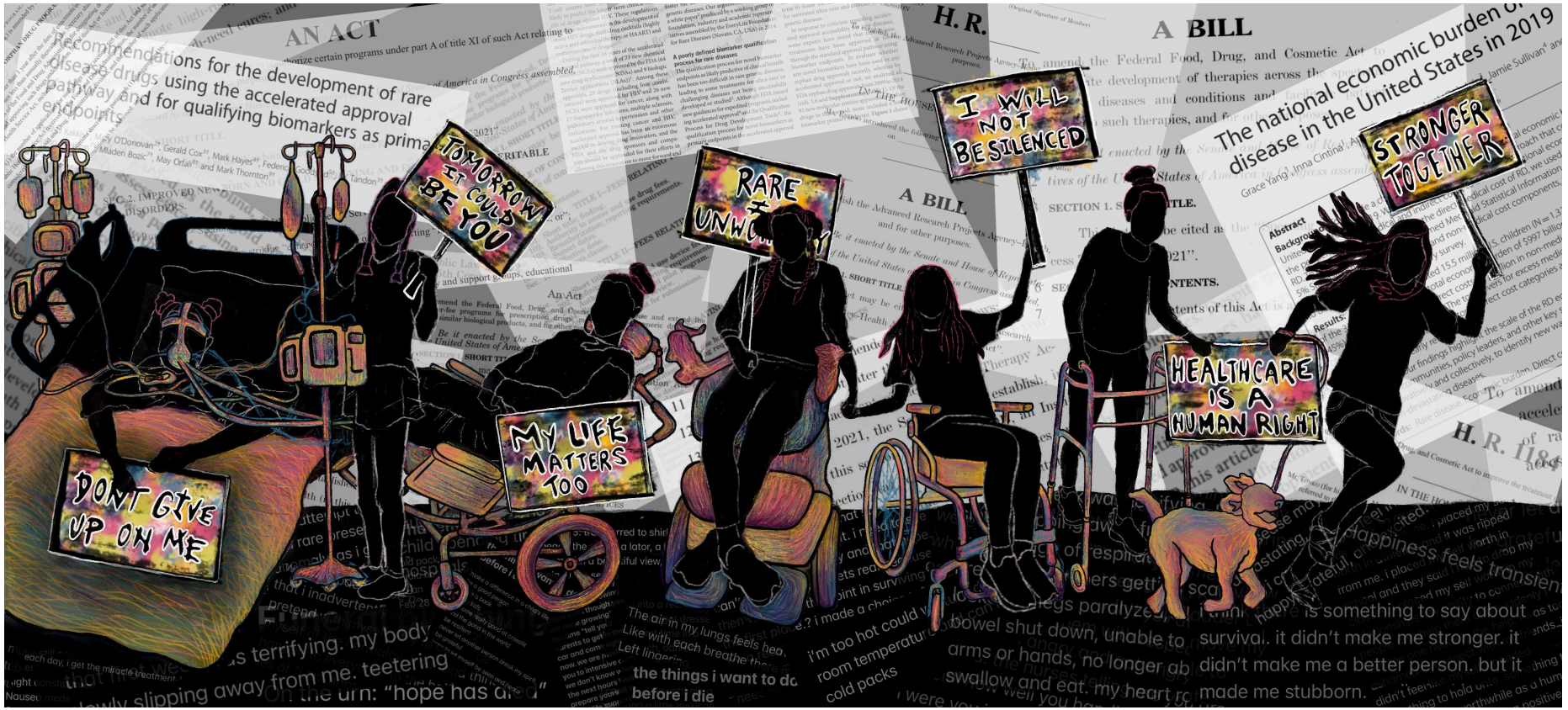
Our "Why"

A Mile in my Shoes – Anneliese Williams, 2022 Rare Artist Finalist



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