Challenges and Opportunities in Drug Development: A Regulatory Perspective

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Strategies to Better Align Investments in Innovations for Therapeutic Development with Disease Burden and Unmet Needs
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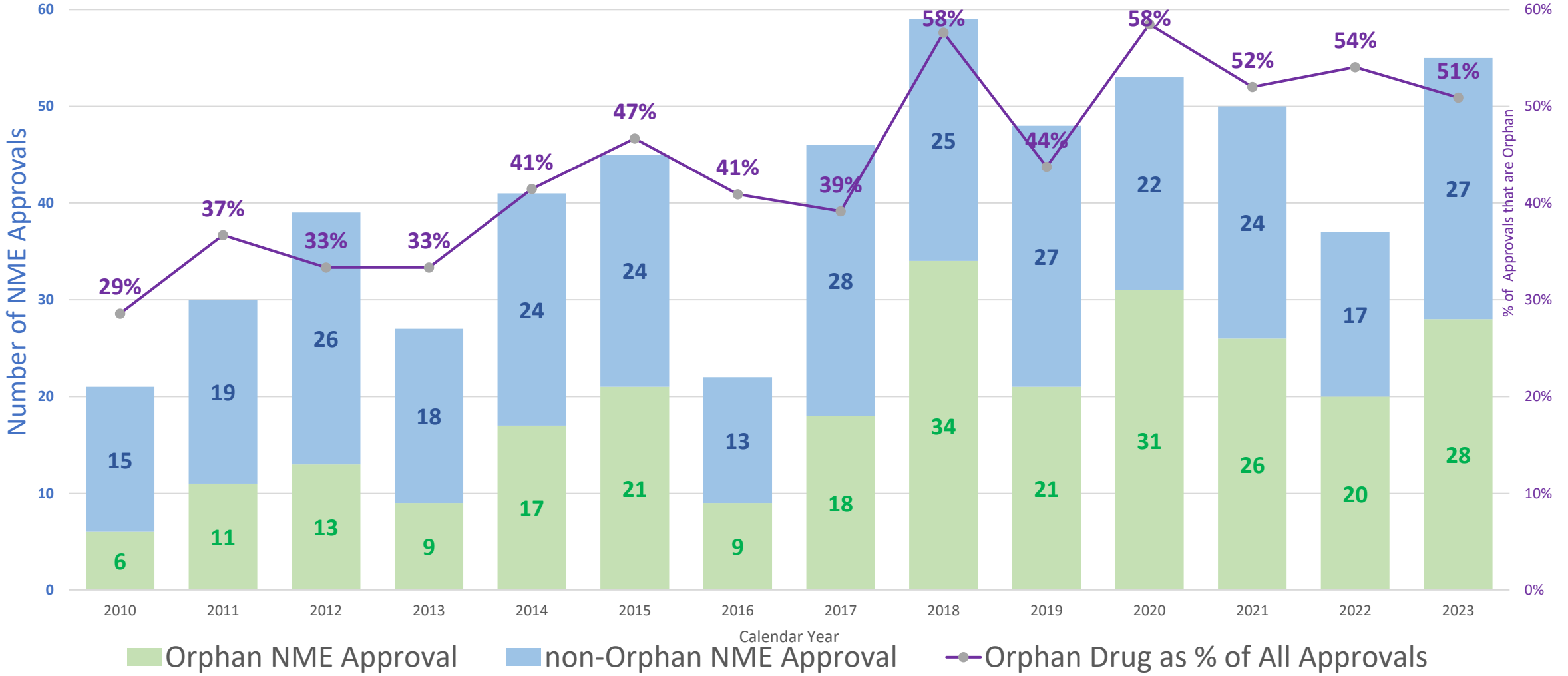
Views expressed are my own and do not represent an official FDA position

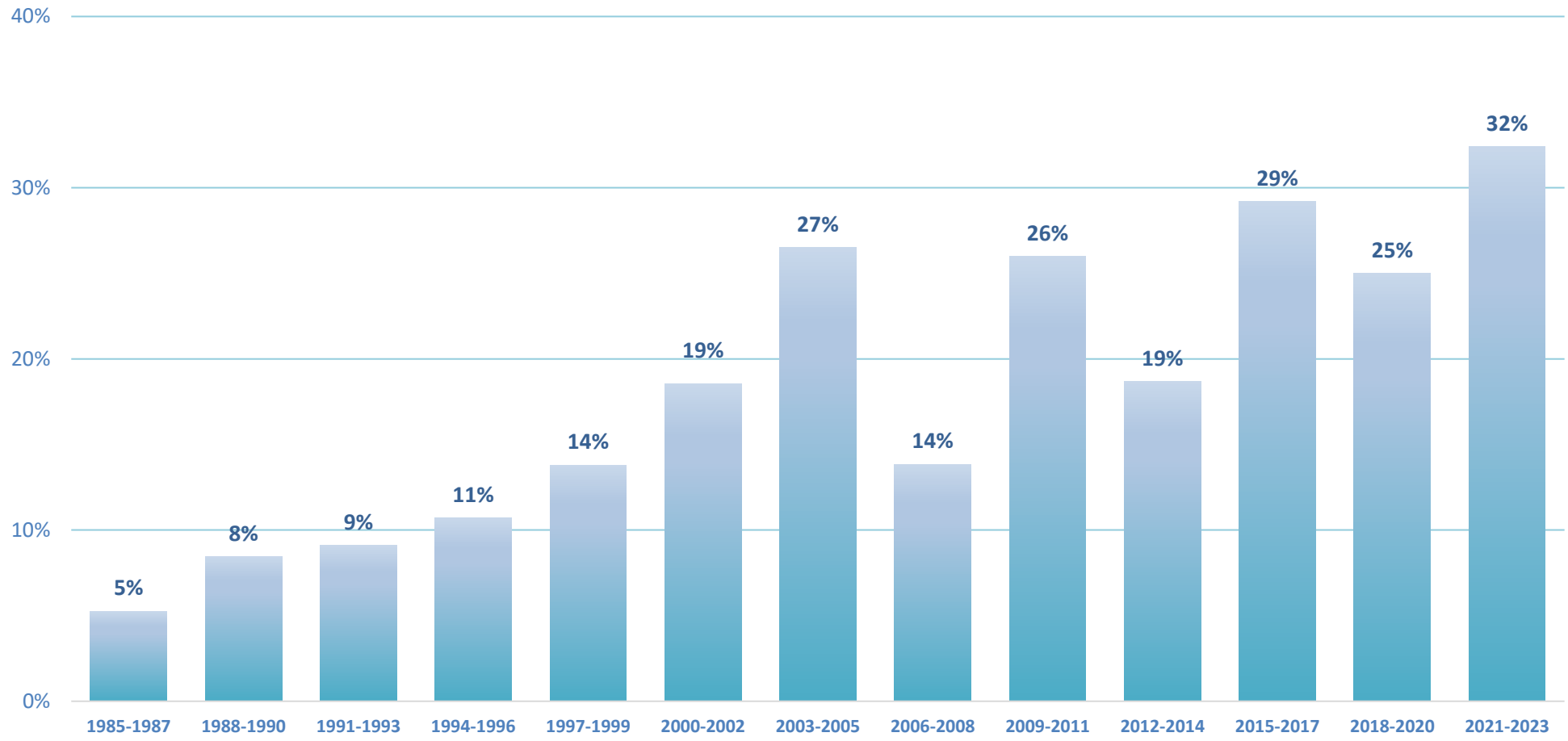
Changes in Clinical, Scientific, Economic Landscape Drive Changes in Drugs Being Developed

- **A shift towards rare disease and narrower population drug development**
- **Targeted populations** based on ability to identify a molecular target, e.g. oncology
- **Multiple approved drugs for common diseases**: competitive markets, narrowing opportunity
- **Evolving science:** rapidly expanding understanding of genetics, genomics, immunology, molecular drivers—the molecular underpinnings of diseases and disease subtypes
- **Many rare diseases with unmet needs**: evolving science providing new targets, and new platforms making them tractable
- **Economic incentives for rare disease drugs:** e.g., orphan exclusivity and others
- **Change in focus for common** chronic diseases on subpopulations / narrower subsets of common diseases
- **New platforms** enabling targeting of previously undruggable targets: siRNA, ASOs, bispecific antibodies, ADCs, cellular or gene therapies

Changing the Landscape: a Steadily Rising Proportion of Novel Drug Approvals That Are Orphan



Biologics as a Percent of Overall Approvals



Elements of Technical and Regulatory Success for a Drug Development Program

- Characterization of the target disease: biology-based vs symptom-based; subgroups; genotypic and phenotypic diversity; natural history
- Whether there is a precedent for drug development, including presence of FDA guidance
- Characterization of the drug's molecular target and mechanism of action
- Strength of translational data (preclinical, exposure-response, surrogates, etc.)
- Availability of Drug development tools such as validated endpoints; established biomarkers, model informed approaches
- Appropriate use of regulatory approval pathways, e.g. accelerated approval
- Program and clinical trial design, including statistical methods, use of RWD etc
- Patient-focused drug development
- Clinical trial recruitment, including diversity

FDA's Expedited Programs to Address Unmet Medical Need in the Treatment of a Serious Condition

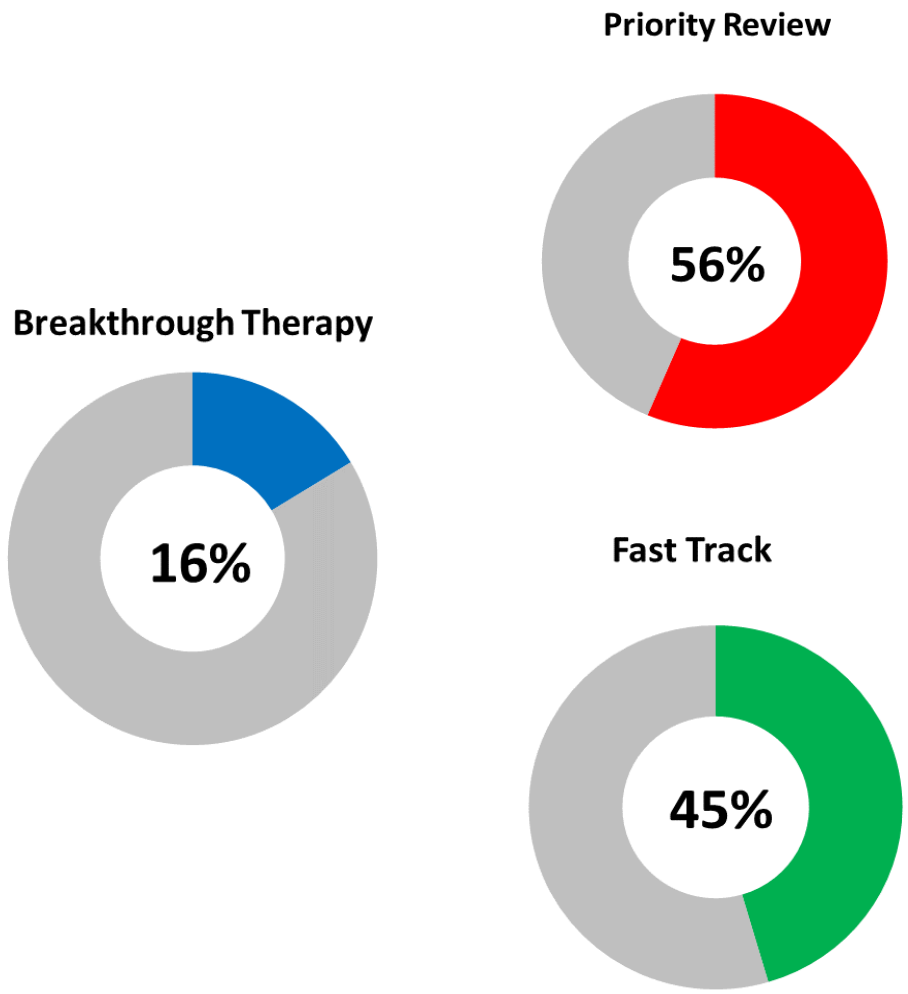
- Eligibility criteria for expedited programs:
  - Serious condition
  - Available therapy (does not include accelerated approval drugs)
  - Unmet medical need
- These criteria are disease-specific
- For many chronic diseases with existing therapies, it is more difficult to identify an unmet need
- Four expedited programs (only accelerated approval is an approval pathway):
  - Fast track designation
  - Breakthrough therapy designation
  - Accelerated approval
  - Priority review

Utilization of Expedited Development and Review Programs for CY2023

Fast track: based upon preclinical or clinical data, or strong rationale

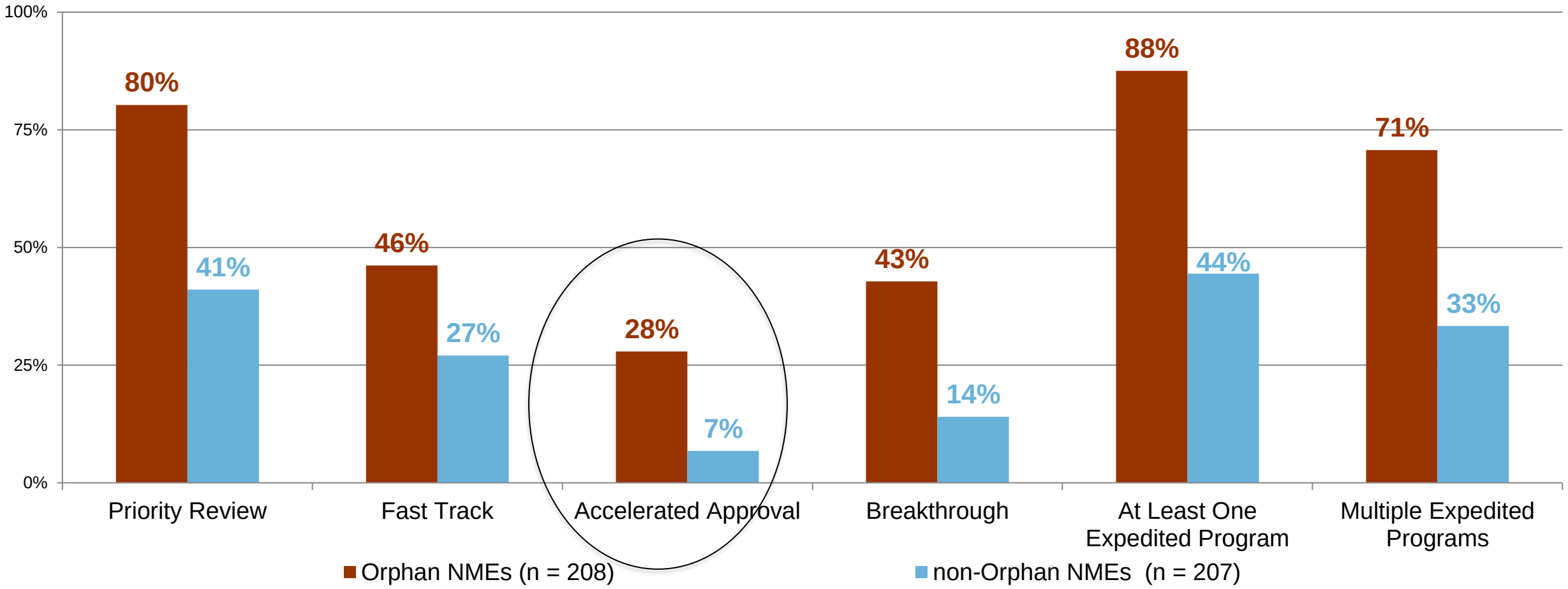
Breakthrough designation: preliminary clinical evidence suggesting substantial improvement

Priority review: drug offers significant improvement; priority review voucher; qualified infectious disease product

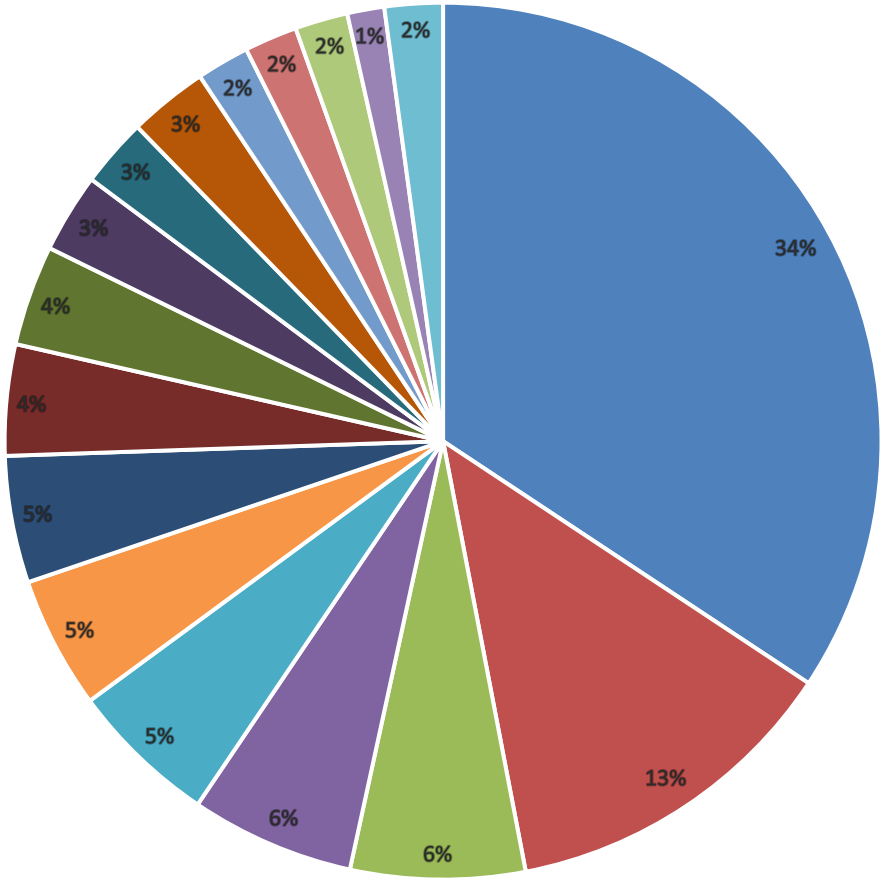


CDER Use of Expedited Programs

NME and New Biologic Approvals CY 2015 - 2023



513 Breakthrough Therapy Designation Requests Granted by CDER Divisions



- Oncology
- Hematologic Malignancies
- Antivirals
- Psychiatry
- Non-malignant Hematology
- Cardiology/Nephrology
- Pulmonology/Allergy/Critical Care
- Dermatology/Dentistry*
- Neurology
- Rare Diseases/Medical Genetics
- Anti-Infectives
- Hepatology/Nutrition
- Rheumatology/Transplant Medicine
- Diabetes/Lipid Disorders/Obesity
- Anesthesiology/Addiction Medicine/Pain Medicine
- Opthalmology
- Other

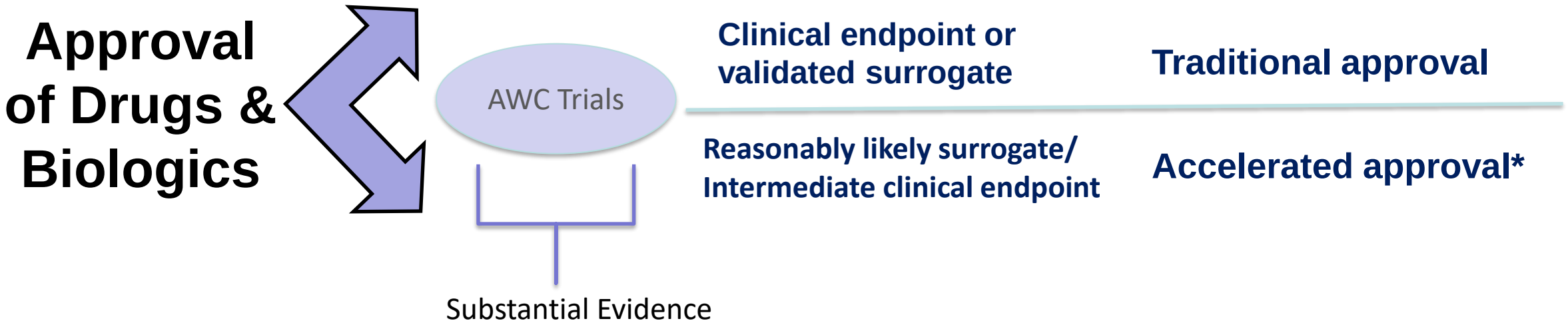
Data as of June 30, 2024

The Breakthrough Therapy Designation was enacted in the Food and Drug Administration Safety and Innovation Act on July 9, 2012.

The Other category for grants includes General Endocrinology, Gastroenterology, Imaging/Radiation Medicine.

*Due to some in-process internal system updates, data on this graph for DDD may appear somewhat different in other settings such as FOIA requests.

U.S. Drug and Biological Approval Pathways



AWC – Adequate and Well Controlled Trials
21 CFR 312.126

* 21 CFR Part 314, Subpart H (for drugs)
21 CFR Part 601, Subpart E (for biologics)
Food and Drug Administration Safety and Innovation Act 506(c)

Patients at the "Center" of Drug Development

Changing Role of the Patient

- Patient at "center" of drug development: "patient-focused drug development": greater participation through the drug lifecycle
- Use of mobile technologies to collect patient-based observations

Objectives of PFDD:

- Patients are experts in their own experience of their disease or condition and the ultimate consumers of medical products
- Patient experience data can inform medical product development and enhance regulatory decision making to address patients' needs

FDA Has Numerous Initiatives Aimed at Spurring Innovation in Drug Development: Some Examples

- FDA Rare Disease Innovation Hub
- CDER Accelerating Rare Disease Cures program
- CDER Center for Clinical Trial Innovation
- CDER Quantitative Medicine CoE
- Platform technology framework
- Advanced manufacturing program, e.g. CDER's Emerging Technologies Program
- Advancing Real-World Evidence program
- Implementation of Clinical Trial diversity plans
- CDER's new drug review modernization initiative
- Modernization of CDER's Advisory Committees
- Modernization of FDA's inspection program

Is there misalignment between drug development innovation and unmet population health needs?

- Factors that may determine success in drug innovation:
  - Inherent characteristics of the therapy: e.g. is there an identified target for the drug and how well does the drug bind to the druggable target
  - Probability of technical success: e.g. clinical trial design; availability of patients for development program; whether RWE is available and of regulatory quality
  - Probability of regulatory success: e.g. applicability of accelerated approval pathway; whether regulatory flexibility can be applied
  - Patient and disease community engagement : BUT drugs that don't work are not patient centric
  - International regulatory convergence: limit unnecessary duplication or custom regulatory requirement
  - Economics: e.g. size of population; reimbursement; statutory financial incentives
- All the factors should be taken into consideration, and there isn't a single "magic wand": for instance, no amount of regulatory flexibility can overcome lack of effectiveness or safety risks that outweigh benefit

Is there misalignment between drug development innovation and unmet population health needs?

- Not surprisingly given these factors, drug development is increasing shifting toward rare diseases, where there is huge unmet need, and targeted molecular therapies, which are often biologics
- But there are notable exceptions, such as novel drug classes aimed at high prevalence chronic conditions associated with high morbidity or mortality, e.g. GLP-1 receptor agonists and obesity; amyloid immunotherapies for Alzheimer's disease
- All the factors have to be taken into consideration, and there isn't a single "magic wand":
  - Regulatory flexibility is an important tool in serious conditions with unmet medical need, but the data must support the statutory requirement of "substantial evidence of effectiveness"
  - No amount of regulatory flexibility can overcome lack of effectiveness or safety risks that outweigh benefit
  - Drug development should take into consideration the patient's perspective, but drugs that don't work or are unsafe are not patient-centric
- All parties, including private industry, government, Congress, payers and regulatory agencies must work together to drive innovation to meet population health needs

Thank You