U.S. FOOD & DRUG ADMINISTRATION

Role of regulatory science in informing regulatory decision making

FDA/MCERSI Hybrid Workshop:

Clinical Pharmacology Guidances Advancing Drug Development and Regulatory Assessment: Role and Opportunities

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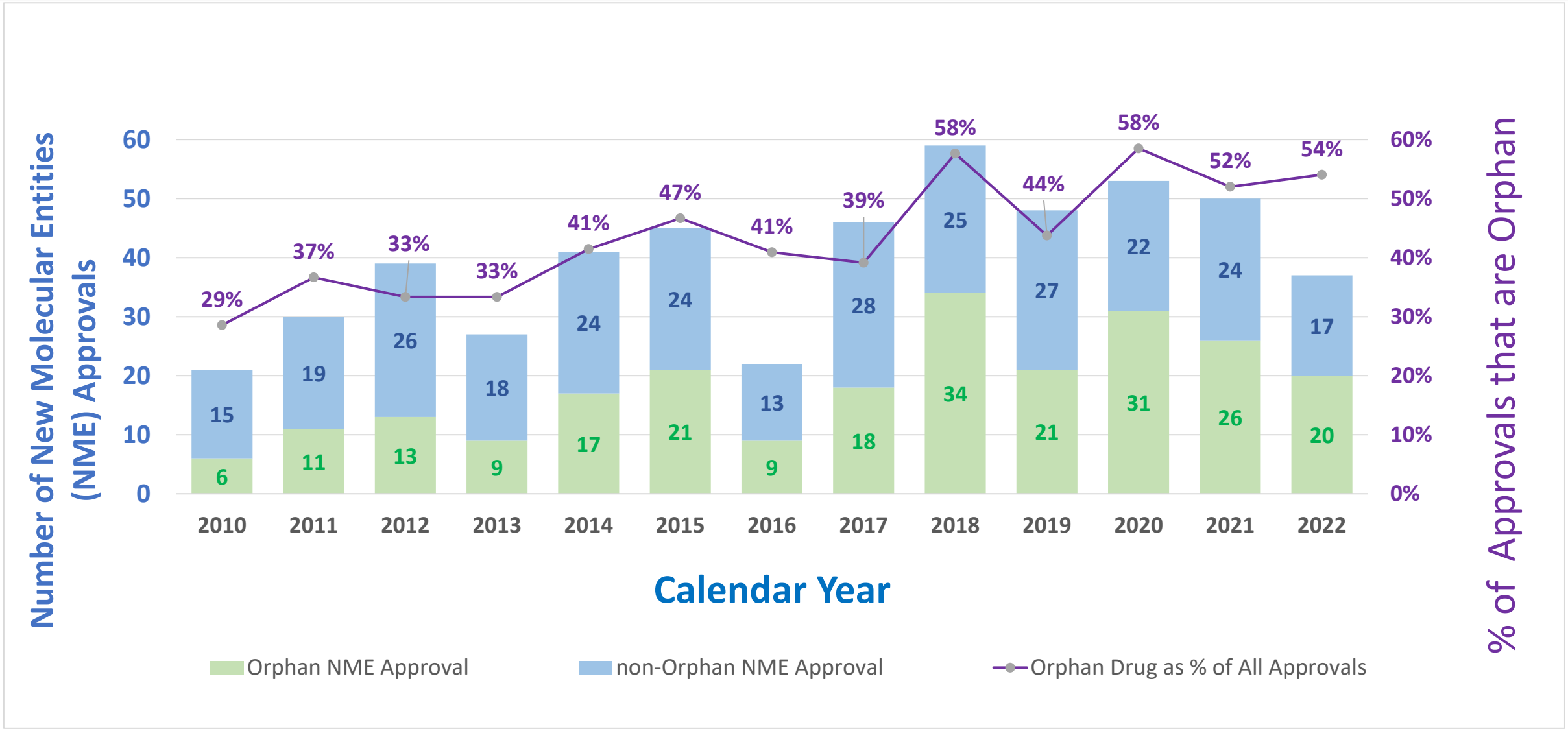
Views expressed are my own, and do not represent an official FDA position

An overview: from the OND perspective

- Changing “context”: changes in the drug development and regulatory landscape
- The challenges of rare disease drug development and regulation: changing needs in drug regulation
- Changes in the approaches to evidence generation for common, chronic diseases
- Filling “gaps” and expanding understanding in areas impacting drug development and regulation: the role of regulatory science

Changing the landscape: a steadily rising proportion of novel drug approvals that are orphan



Changes in the clinical, scientific and economic landscape drive changes in drugs being developed

A shift towards rare disease and narrower population drug development

- **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

For **common chronic diseases**: an emphasis on efficiency, effectiveness, and innovation in evidence generation, expanding experience across populations

The challenges of rare disease drug development

From common chronic diseases

- **Large populations**, so recruitment generally not a challenge
- Standard approach of **2 large, adequate and well-controlled trials** to support effectiveness and safety
- Wide range of disorders: symptomatic non-progressive, risk factor modulation (e.g., LDL-C), to serious, progressive fatal diseases
- Reasonably well understand natural history
- FDA **guidances** usually available – and **precedent** from prior programs informs study design
- **Endpoints generally well accepted** and standardized (e.g., LDL-C, BP, A1C, FEV1/exacerbations, PASI, etc.)

To rare disease development challenges

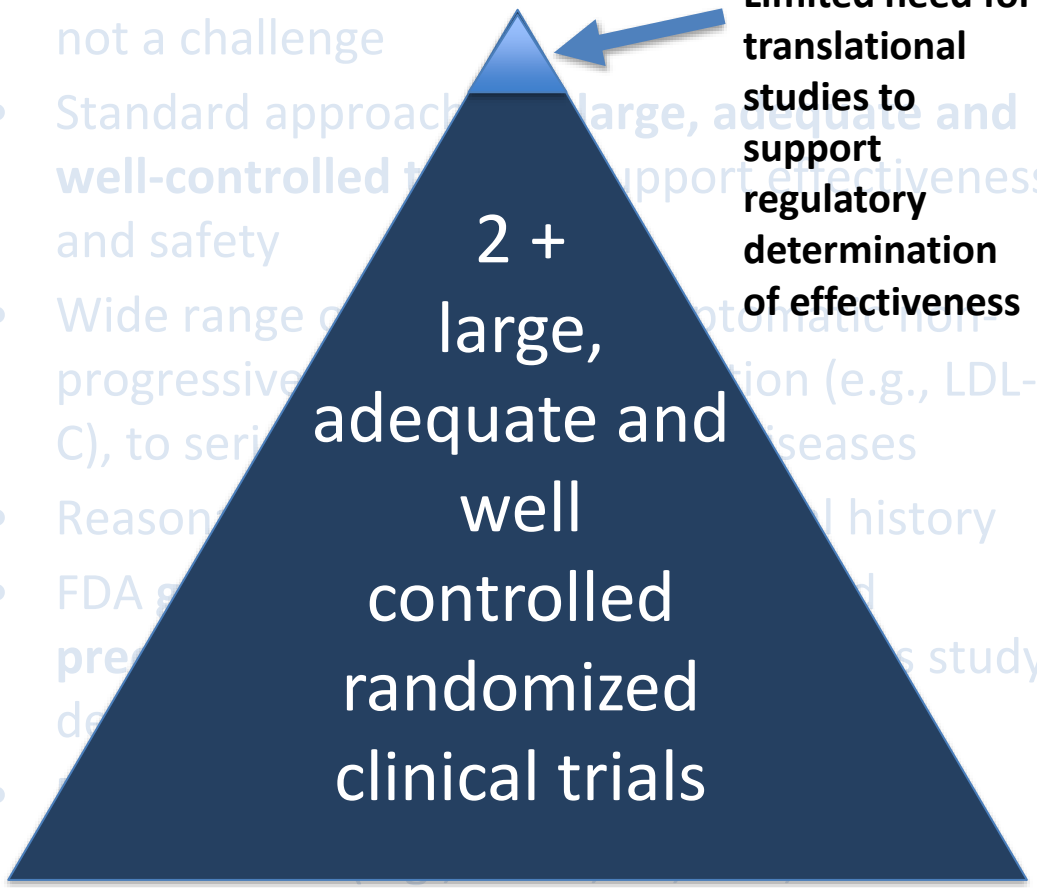
- **Small populations** with difficult recruitment
- Requires **flexibility in study designs**, and limited ability for replication
- Often **progressive**, **serious**, **life-limiting and life-threatening** and lack **approved therapy**
- Lack of **precedent** for drug development – often no FDA guidance for a specific rare disease
- **Genotypic and phenotypic** diversity – **heterogeneous** presentations, courses, and outcomes, **natural history** often known
- **Drug development tools** such as validated **endpoints,** established **biomarkers** often lacking
- **Ethical** considerations for children in clinical trials – impact trial design options

The challenges of rare disease drug development: the need for expanding our understanding

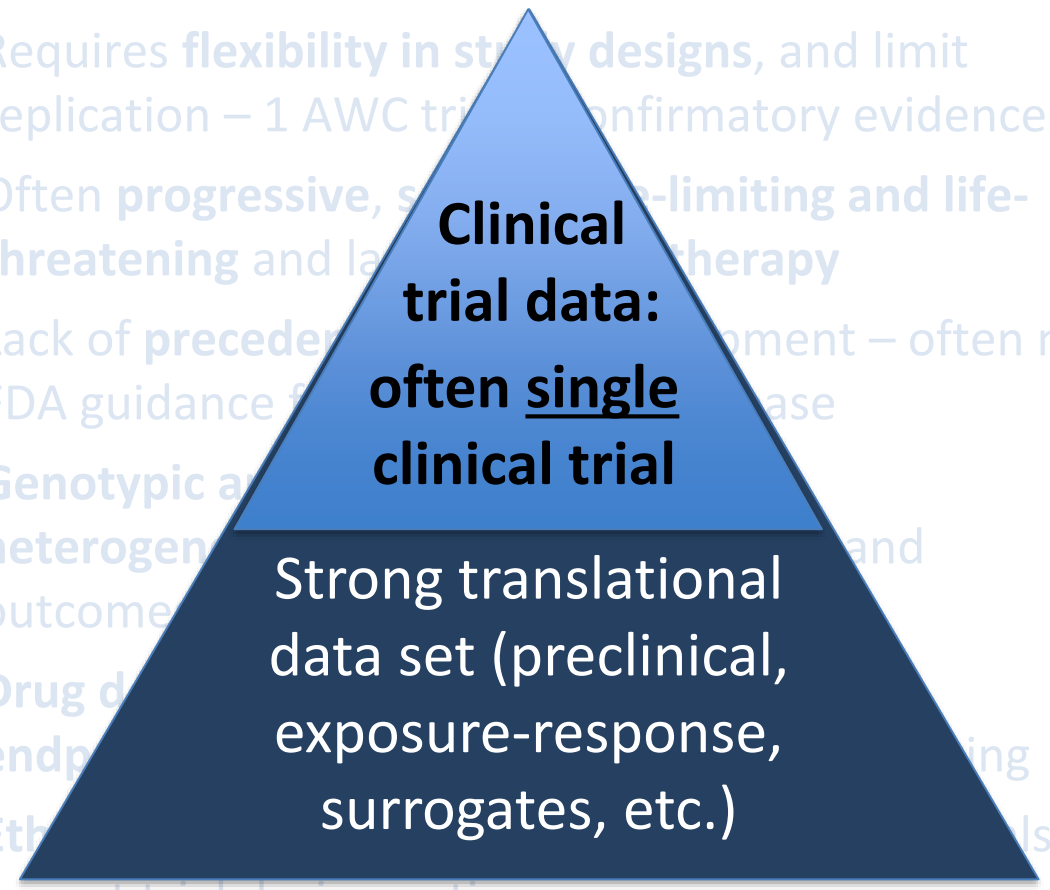
	To rare disease development challenges
Novel trial designs fit for purpose for small population programs; use of M&S to maximize use of clinical data	• **Small populations** with difficult recruitment • Requires **flexibility in study designs**, and limited ability for replication
Assessment of key disease burdens and outcomes, guidance development	• Often **progressive**, **serious**, **life-limiting and life-threatening** and lack **approved therapy** • Lack of **precedent** for drug development – often no FDA guidance for a specific rare disease
Support for natural history studies, aggregation of clinical data to support understanding of disease	• **Genotypic and phenotypic** diversity – **heterogeneous** presentations, courses, and outcomes, **natural history** often known
Need for novel drug development tools, especially common elements across rare diseases: COAs, surrogates, biomarkers	• **Drug development tools** such as validated **endpoints,** established **biomarkers** often lacking • **Ethical** considerations for children in clinical trials – impact trial design options

The challenges of rare disease drug development

Common disease drug development

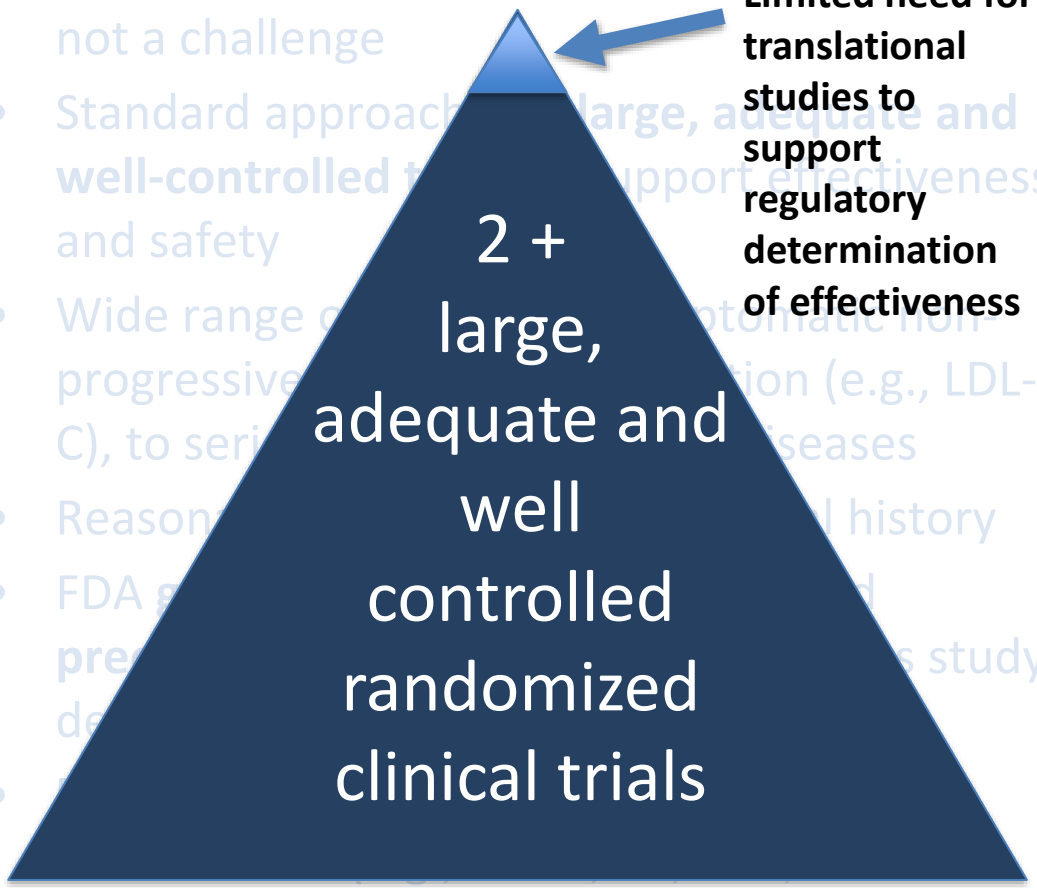


Rare disease drug development

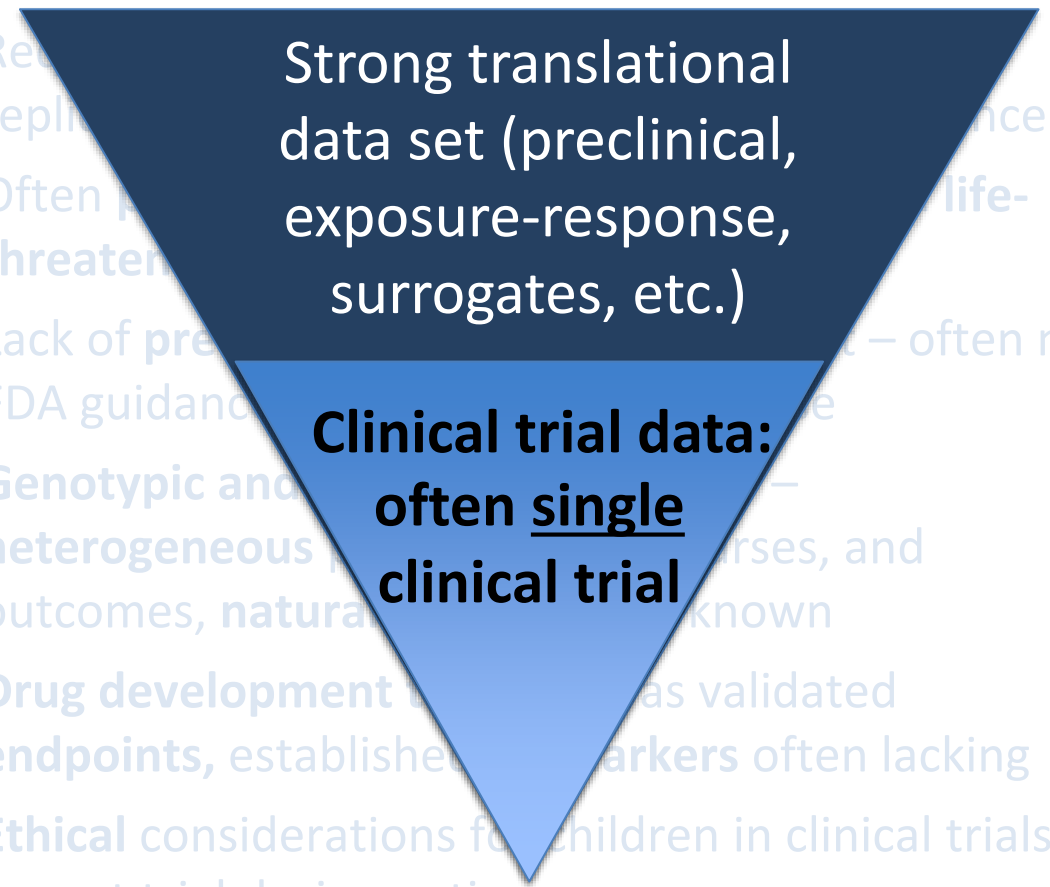


Rare disease drug development stands "classic" drug development on its head

Common disease drug development



Rare disease drug development



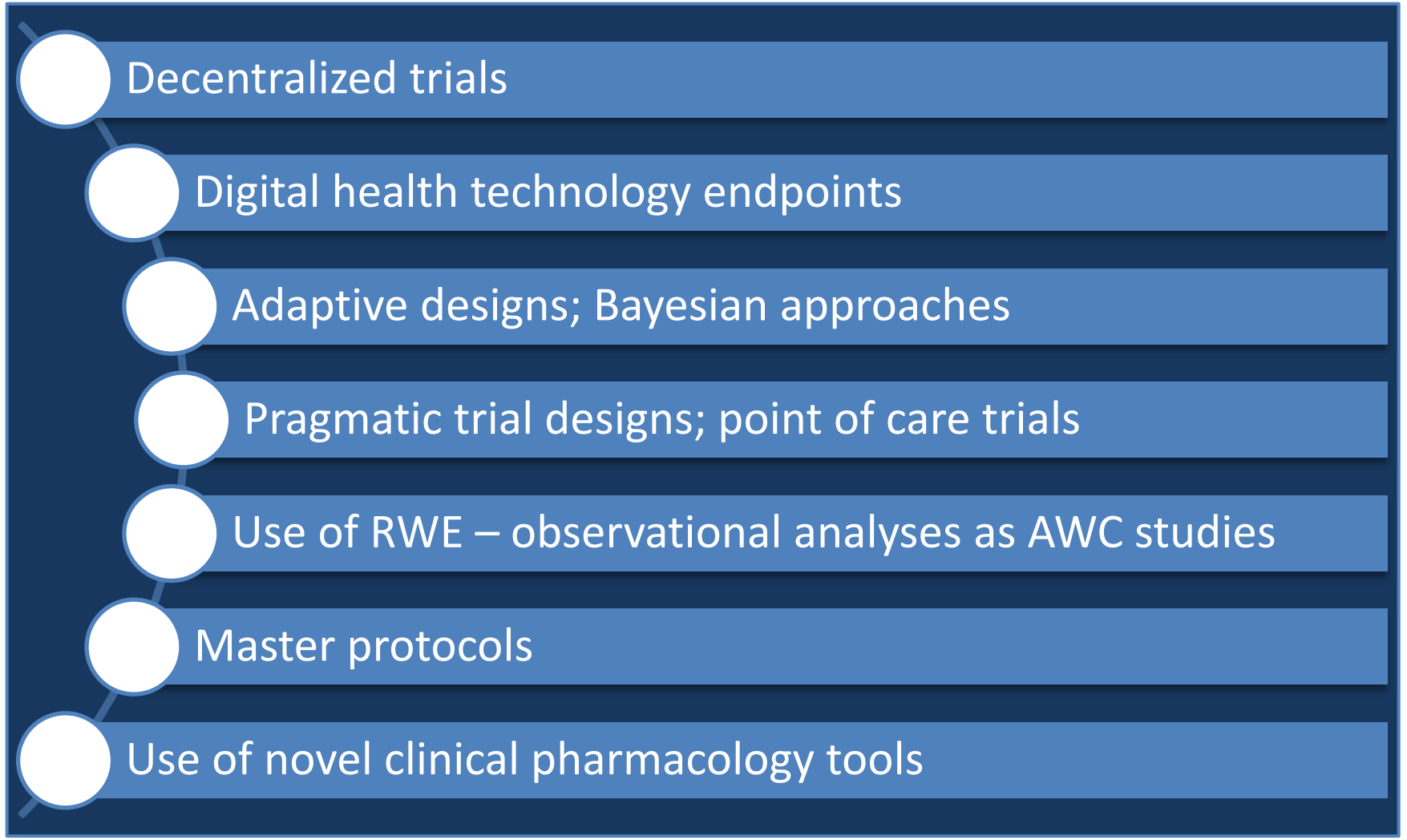
For common chronic disease, an increased focus on novel approaches or subpopulations

- **Changing focus** in areas of development
  - Many common diseases still with inadequate treatments: opportunities for differentiated drugs: e.g., T2DM, obesity, CHF, AD
  - Focus on treatments for common diseases **subpopulations**
- Focus on clinical program **efficiency and effectiveness**
  - Decentralized trials
  - Use of new tools: digital health technology
  - Use of novel trial design and analysis: adaptive designs, platform trials, Bayes
  - Use of large simple trials, trials with pragmatic elements, master protocols
  - Use of RWD/RWE for label expansion
  - Improved use of clinical data to support regulatory decisions: advances in clinical pharmacology: MIDD, modeling and simulation

The changing “face” of clinical trials

- Decentralized trials
- Digital health technology endpoints
- Adaptive designs; Bayesian approaches
- Pragmatic trial designs; point of care trials
- Use of RWE – observational analyses as AWC studies
- Master protocols
- Use of novel clinical pharmacology tools

The changing “face” of clinical trials



Need for expanding our understanding across all these new approaches to support appropriate guidance development, regulatory advice and decision making – *the need for regulatory science*

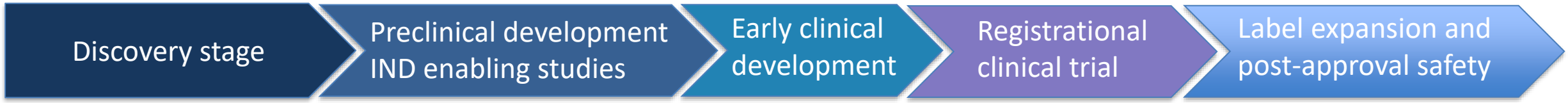
What is “regulatory science”?

- Science focused on improving efficiency and effectiveness of drug development, enhancing FDA’s ability to guide and regulate IND development, FDA’s review of applications (clinical and quality), and FDA’s post-approval safety management

What is “regulatory science”? (cont.)

- A few examples of areas or regulatory science:
  - Developing methodologies and support for in vitro and non-clinical drug assessments
  - New drug development tools: biomarkers, surrogates, clinical outcome assessments
  - Enhanced methodologies to assess endpoints
  - Developing new assay methodologies to assess product quality
  - improving trial design approaches and methodologies – especially in new areas of development
  - Improving approaches to analysis of clinical trials: use of Bayesian statistics, analytic approaches to endpoints in both common and in rare diseases
  - Enhancing methodologies to expand and enhance analytic approaches to large clinical datasets: modeling and simulation, MIDD
  - Enhancing approaches to post-market safety management: e.g., REMS

The scope of regulatory science research spans drug development



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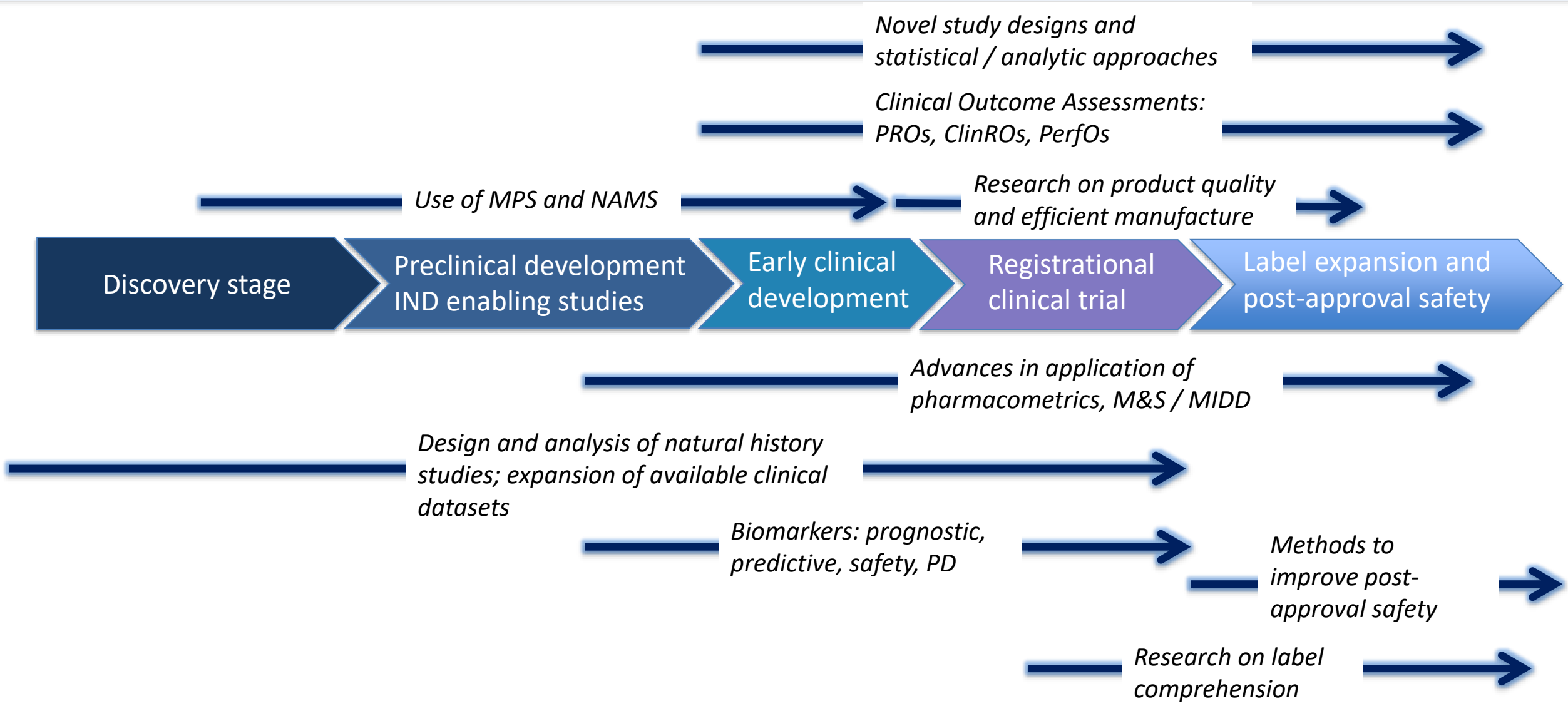

Regulatory research: collaborative examples

Ion Channel Data Standards for Model-Informed Proarrhythmia Risk Prediction Under the Comprehensive in vitro Proarrthymia Assay (CiPA) Initiative

Division of Cardiology and Nephrology (DCN)
Internal review tools

MIDD in the Evaluation and Development of Neurological Drug Products
Office of Neuroscience (ON)

Identify Challenges and Research Frequently Encountered Issues While Combining Data across Multiple Studies/Sources

Division of Bioinformatics, Research, and Biomarker Development (DBIRBD)
Internal review tool

Assessment of Physiologically Based Pharmacokinetic Modeling for Predicting Fetal Exposure to Maternal Drugs

The Prevalence of Psychiatric and Chronic Pain Comorbidities in Fibromyalgia: an ACTTION Systematic Review

Kidney Transplant Biomarker Qualification: A Reasonably Likely Surrogate Endpoint for Five-Year Risk of Allograft Loss
Division of Rheumatology and Transplant Medicine (DRTM)

Pregnancy and Lactation Labeling Rule (PLLR): Health Care Provider Testing to Improve Health Communications Related to Lactation
Division of Pediatric and Maternal Health (DPMH)

Assessment of Physiologically Based Pharmacokinetic Modeling for Predicting Fetal Exposure to Maternal Drugs

Minocycline Pharmacodynamics Against *Stenotrophomonas maltophilia* in the Neutropenic Murine Infection Model: Implications for Susceptibility Breakpoints

Use of Quantitative Modeling to Support Pediatric Extrapolation
Division of Pediatric and Maternal Health (DPMH)

Development of a Toolbox of Clinical Outcome Assessments for Assessment of Neuropsychological/Neurodevelopmental and Cognitive Outcomes

Development of a Model for Predicting Drug-Induced Liver Injury (DILI) Risk in the Investigational New Drug (IND) Phase of Drug Development

Division of Hepatology and Nutrition (DHN)
Internal review tool

Patient-Reported Outcomes in Pediatric Cancer Registration Trials: a U.S. Food and Drug Administration Perspective

What are some of the outcomes of regulatory science research?

- Guidance development: draft, revisions of guidances, final guidances
- Enhancing the advice FDA provides during IND development
- Enhancing FDA's review of product quality issues
- Enhancing FDA's review of applications
- Increasing availability of DDTs
- Methodologies that enhance evidence development to support regulatory decisions and actions – across a wide spectrum of decisions
- New resources that support drug development for diseases without adequate treatments

How does OND assess the value of our research outcomes?

Least common

≤ 10% of outcomes reported/FY

Highest value

Very mission relevant; directly facilitate new drug approval

- Supports a guidance
- Supports novel trial design, endpoint, analytic approach
- Label change
- Sponsor uses research finding to enhance development efficiency or effectiveness
- Supports a regulatory decision

Summary: the need for regulatory science

- **Drugs for rare diseases** require different development and regulatory approaches
  - Better disease understanding: NH studies
  - Innovative trial designs
  - Enrichment approaches
  - Novel endpoints: COAs and surrogates
  - New analytic approaches
  - Enhanced efficiency
- For common diseases: new approaches to **evidence generation** to support regulatory decisions
  - Efficiency in evidence generation – use of existing data (RWD/RWE)
  - Improved analytics of RWD/RWE
  - Simplified trial designs – “simple” / “pragmatic” designs
  - Trials embedded in practice – broadening recruitable population, enhancing diversity

Thank You