From Bench to Bedside:
How Regulatory Science and Patient Perspective Drive Smarter Drug Development?

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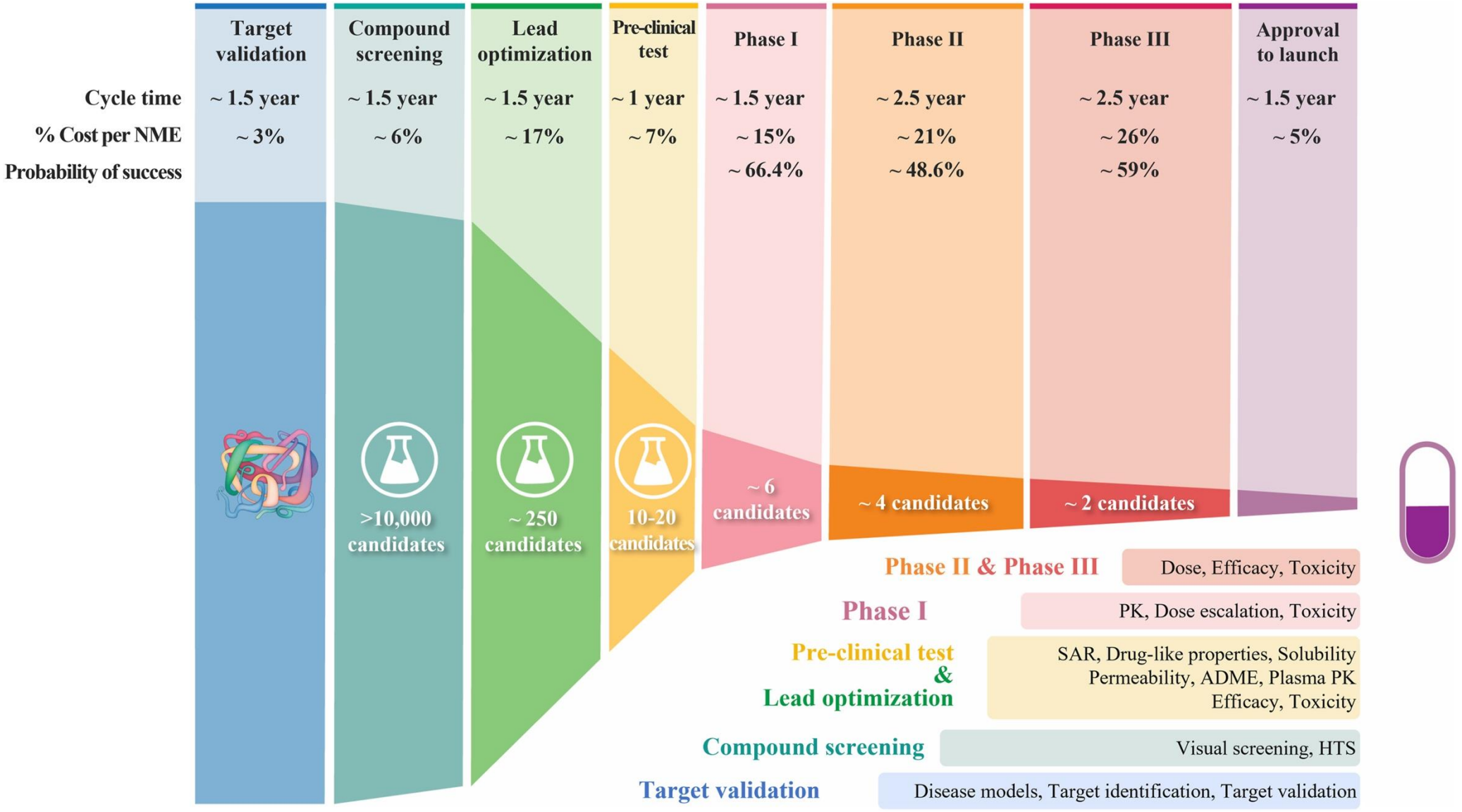
Disclaimer

The views and opinions expressed in this presentation are my own and do not necessarily reflect the views and policies of the FDA.

Presentation Outlines

- Scientific and policy challenges of the drug development process
- Introduction of regulatory science and its role in the different phases of the process
- Risk-benefits framework as the foundation of the regulatory decisions
- Approaches and processes of including patients' perspectives
- Q/A

The Drug Development Funnel: Why 90% of Potential Drugs Fail



Sun, et al. Act Pharm. Sinica, 2022

The Big Picture Of Scientific Challenges in Drug Development

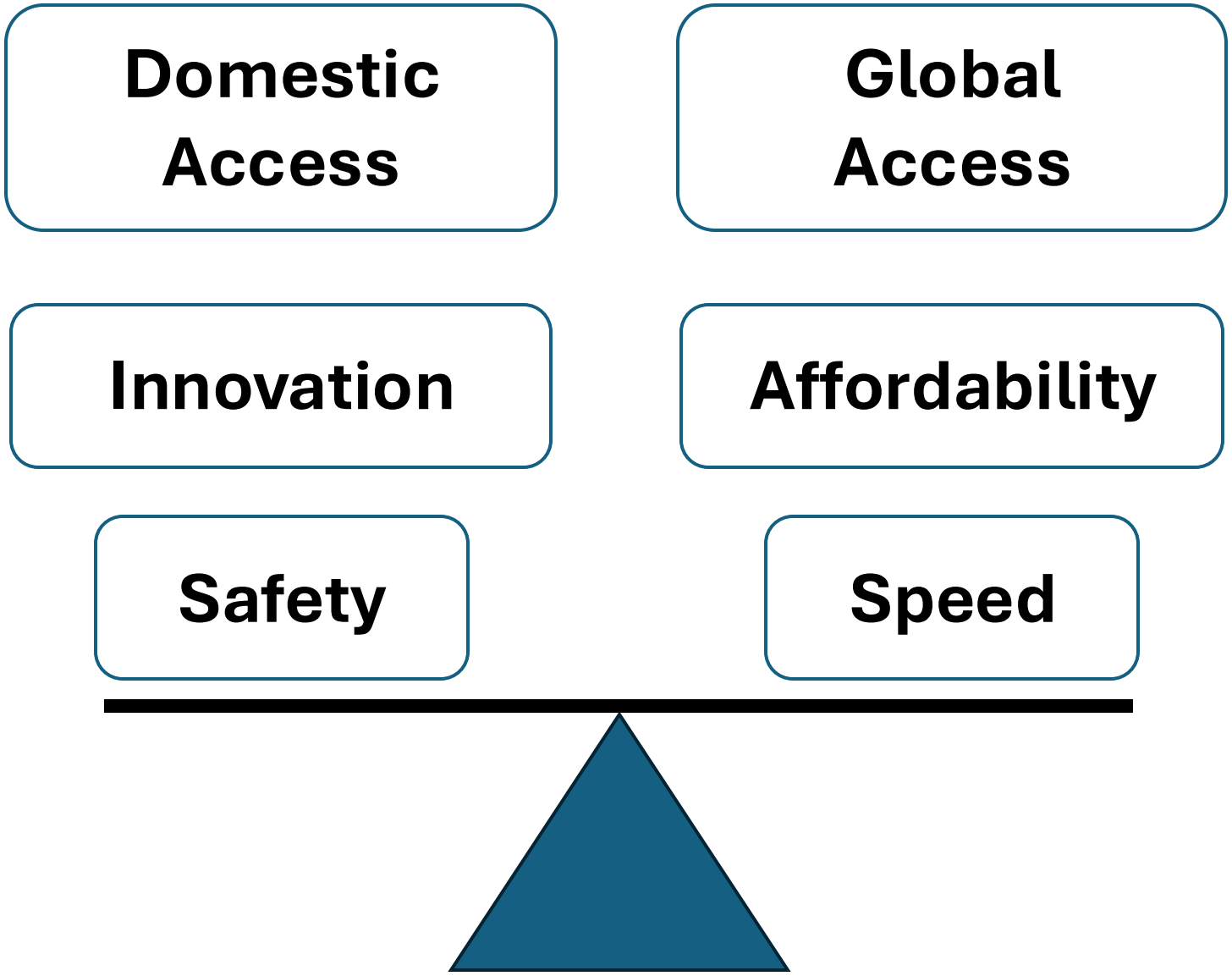
- **High rates of failure**
  - Failure is the norm, not the exception
  - 90% of drug candidates fail in clinical trials
    - Lack of efficacy (no benefit to patients)
    - Safety concerns (unmanageable toxicity and side effects)

- **It is a marathon, not a sprint**
  - 10-15 years

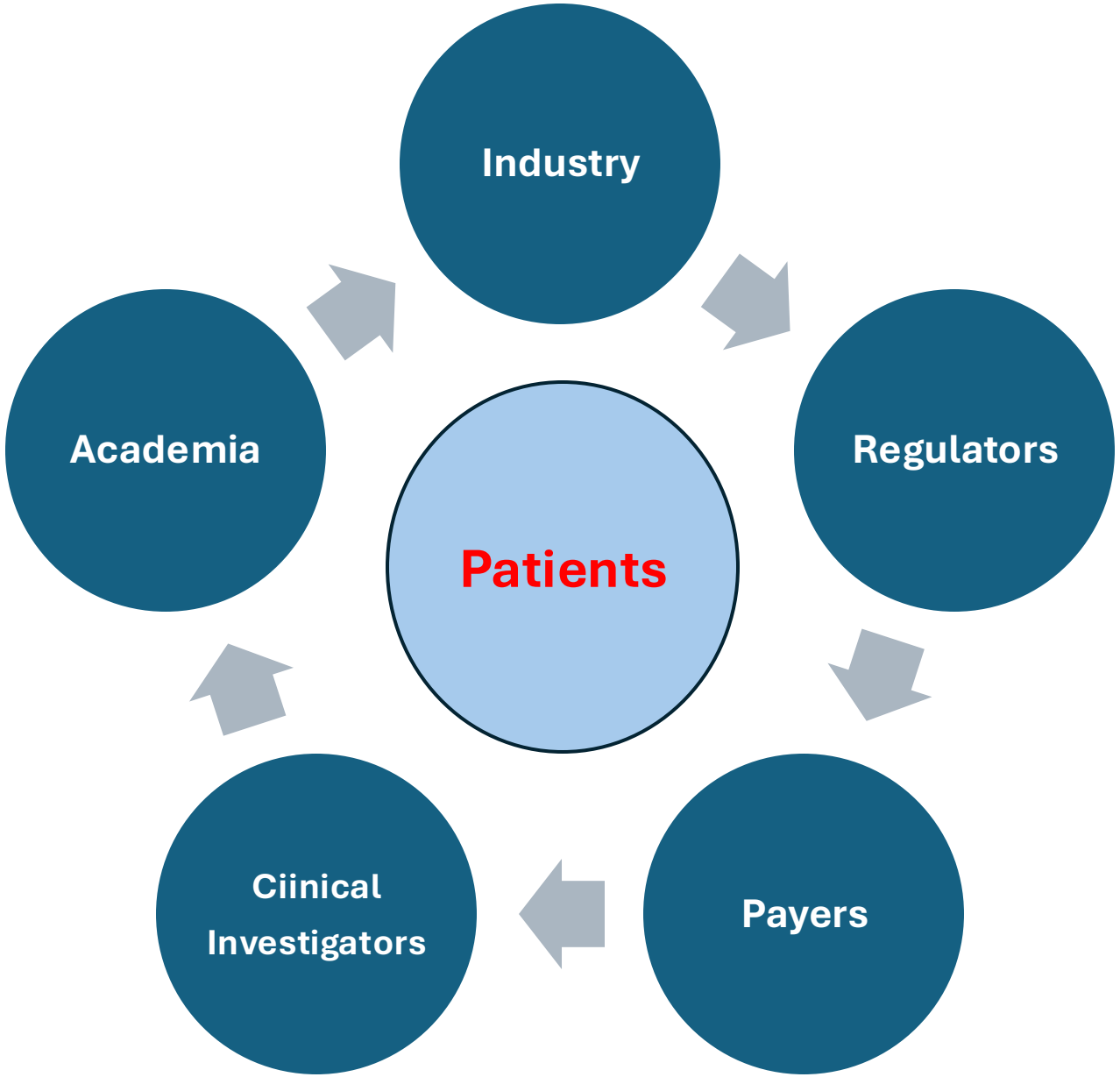
- **Complexity of human biology**
  - Diseases have many subtypes
  - Animal vs. human

- **Unpredictable roadblock**
  - Unknown rare side effects

Policy Challenges of the Durg Development Process



Collaboration is Essential to Create a More Efficient Ecosystem for Innovation



How Can Regulatory Science Promote Collaboration Between all Stakeholders in the Drug Development Ecosystem?

This role relies on 3 principles

1. **Shared authority**
   Regulatory science creates a system where knowledge is co-created and vetted by a broader ecosystem of experts.
   A paradigm shift in authority, regulators don't have near-exclusive power on validity

2. **Co-manage uncertainty**
   Regulatory science transforms uncertainty from a barrier into a managed variable
   This process builds trust by ensuring everyone is aware of the knowns and unknowns

3. **Participatory governance**
   RS actively integrates diverse perspectives into regulatory decision-making
   This engagement deepens the legitimacy and the impact of the regulatory outcomes

Regulatory Science:
A Common Ground for Safer and Smarter Drug Development

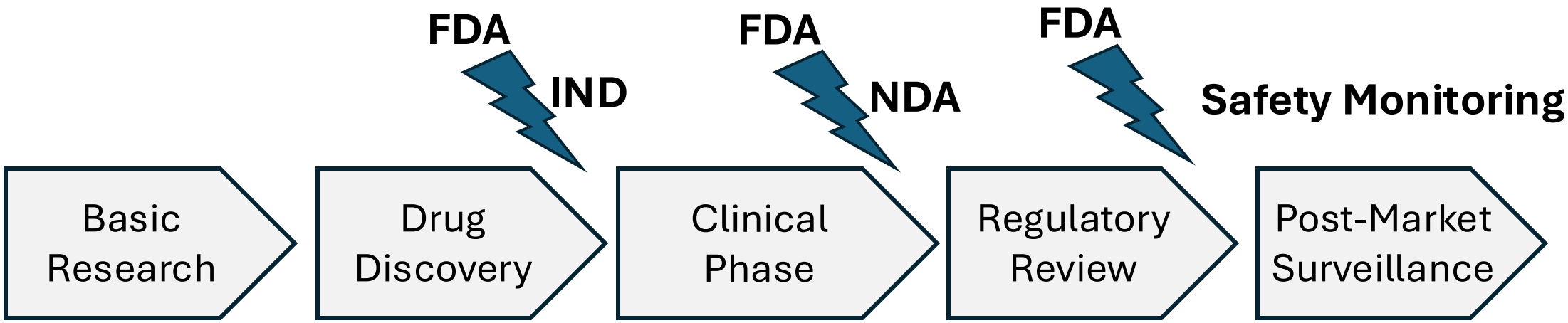
- Regulatory science is the science of the development and application of new tools, standards, and approaches to assess the safety, efficacy, quality, and performance of medical products.

- It is integrated into each stage of the drug development process to improve efficiency and reduce uncertainty.

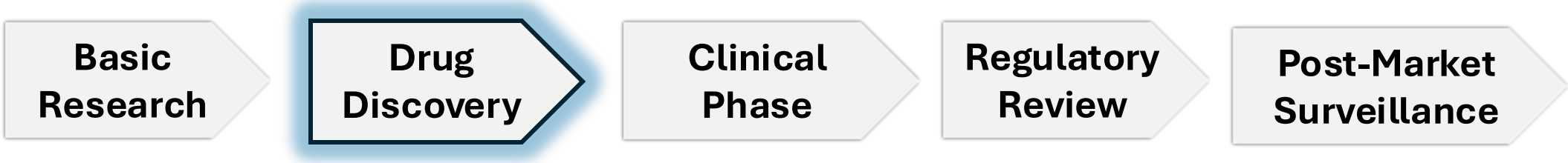
- It is not just about following existing rules, it's about improving the rules themselves by creating a better scientific foundation for regulatory decisions.

- The field bring together science, policy, and law to protect and promote public health.

Regulatory Checkpoints of the Drug Development Process



Applications of Regulatory Science in Drug Discovery



Regulatory Science can modernize research techniques to improve:

- **Efficacy** (better predict a drug's potential effect)
  - Biomarker discovery and qualification

- **Safety (**better predict drug toxicity)
  - Modernizing toxicology testing (New Alternative Methods initiative)

Regulatory Science Supporting Biomarkers Development and Qualification

What is a biomarker?

Defined as a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic (disease-causing) processes, or responses to a therapeutic intervention (like a drug).

What is the role of biomarkers in the drug development process

Biomarkers are critical tools that help speed up and make the drug development process more efficient, and help target treatment to individual patients (precision medicine)

Examples of biomarkers used in Oncology Drugs

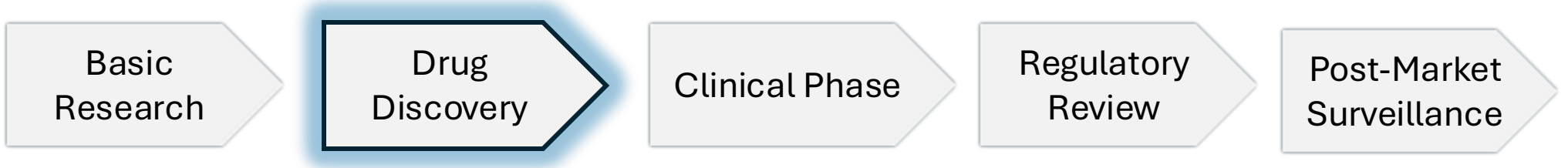
- **HER2 for breast cancer**
  - FDA and sponsors worked together to establish the link between HER2 overexpression and response to drugs, leading to a biomarker-guided strategy

- **KRAS mutation in colorectal cancer**
  - A predictive biomarker for metastatic cancer
  - Allows clinicians to identify patients who will not benefit from anti-EGFR therapies

- **Companion diagnostics (CDx)**
  - Most modern oncology drugs depends on a companion diagnostics test
  - Regulatory science guide the co-development (drug and devise) and evaluation

Regulatory science improves the biomarker development process by increasing efficiency, reducing uncertainty, establishing standards and encouraging collaboration.

Applications of Regulatory Science in Supporting NAMs, Intro.



New Alternative Methods (NAMs)

- Innovative technologies reshaping drug development by providing human predictive data
- Aims to Replace, Reduce and Refine animal testing

- In-vitro models
  - 2D cell cultures and 3D Organoids
  - Organ-on-a-Chip (Microphysiological Systems).
  - They mimic organ-level function and tissue-tissue interactions

- In-Silico approaches
  - Computational modeling (ML and AI)
  - Predicts toxicity, PK, PD based on chemical structure and existing biological data

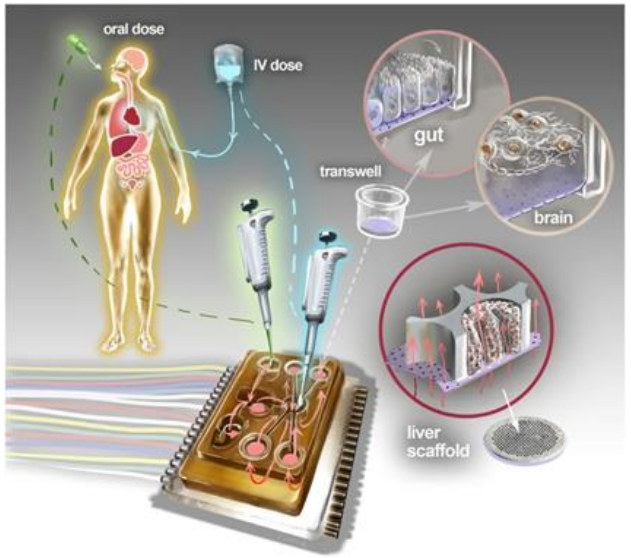
How NAMs Can be Used in Drug Development?

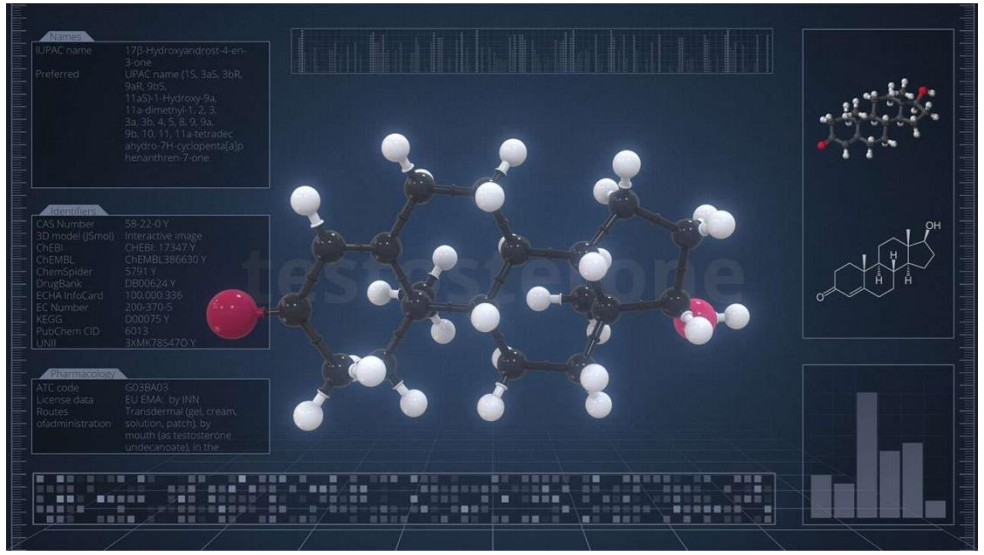
- **Early screening**

  - Rapid, high-throughput toxicity screens allow elimination of unsafe compounds before animal or human testing

- **Mechanism of action**

  - can help determine how drugs interact with human tissue, predicting complex responses undetectable in animal models





Examples of NAMs Applied in Oncology Drug Development

- **Organoids and Microphysiological Systems**

  - Patient-derived organoids created from tumor tissue removed from patient during surgery.
  - Allows researchers to test a variety of drugs on a tumor model
  - Predict drug response before treating the patient
  - Help physicians select the most effective therapy

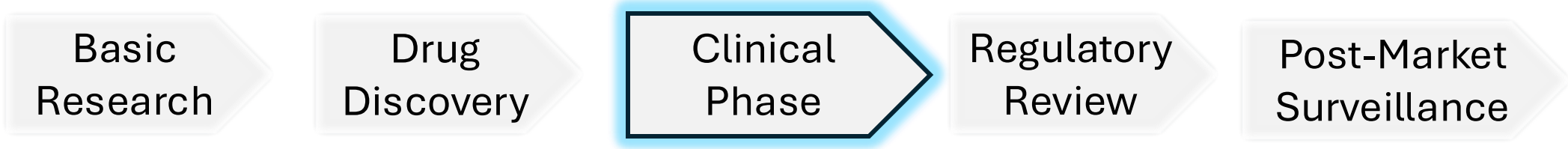
- **In Silico computational model and AI**

  - Allows identification of new therapeutic targets and disease pathways associated with a specific tumor
  - Screen millions of compounds in a fraction of the time vs. traditional screening methods
  - Optimize discovery phase (shorter and less expensive)

Role of Regulatory Science in Advancing NAMs Technologies

- **Improving Predictive toxicology**
  - Provides new tools that improves safety and efficacy predictions
- **Provides the foundation for evaluating the reliability of the NAMs technologies**
  - Assessing the ability of Organ-on-a-Chip devices to model specific organ response (lung, kidney, heart)
- **Establishing standards and qualification**
  - Help sets the qualification standards
  - Ensure that new methods are robust enough for regulatory review and are only used for their content of use

Applications of Regulatory Science in Clinical Phase



- The standard clinical trials design follow a rigid, pre-set protocol that is slow and expensive

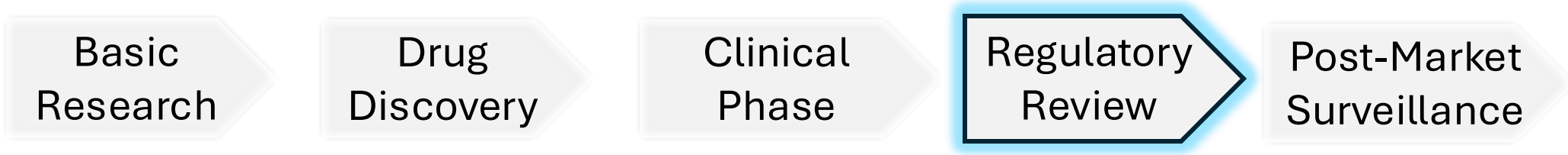
- Regulatory science helps design more efficient and informative clinical trials, including, the adaptive clinical trial, which enables the use of accumulating data to prospectively make changes to the trial design.

- RS supported the design and review of the adaptive clinical trials by:
  - Establishing new standards
  - Address statistical concerns
  - Ensuring trial integrity and transparency
  - Promoting regulatory engagement

Examples of Adaptive Trials in Oncology

- **I-SPY 2**
  - One single protocol for evaluating multiple drugs simultaneously
- **Basket Trials**
  - Same drug used in patients with different cancer types, share same mutation
- **Umbrella trials**
  - Test different drugs for a single type of cancer

Applications of Regulatory Science in Drug Review Process



- RS provides the **tools** and **evidence** to make critical safety and efficacy decisions
- **Risk-benefit analysis** is an evidence-based approach to support regulatory decision

The Risk-Benefit Framework: A Foundation of the Regulatory Decision

- The framework is the core principle guiding the FDA's drug review process
- FDA must determine if the drug's potential benefits outweigh its known and potential risks
- The framework is a structured narrative-based format that ensures consistency, transparency, and clarity of the review process
- The framework is a tool for organizing the evidence and documenting the reasoning for regulatory decisions

Dimension	Evidence and Uncertainty	Conclusion and Reasons
Analysis of Condition		
Current Treatment Options		
Benefits		
Risk and Risk Management		
Conclusion Regarding Benefit-Risk		

The Risk-Benefit Framework: Key Components

	Dimension	Evidence and Uncertainty	Conclusion and Reasons
Therapeutic Context	Analysis of Condition		
	Current Treatment Options		
Analysis of Benefits and Risks	Benefits		
	Risk and Risk Management		
	Conclusion Regarding Benefit-Risk		

Including Patients Perspectives During the Drug Development Process

- Patient engagement is mandated by the U.S. Congress through the FDA Safety and Innovation Act (**FDASIA**) of 2012

- FDA established the Patient-Focused Drug Development (PFDD) Initiative

- A systematic process for gathering patient input as a priority for regulatory decision making

- Ensures that patient's voice, experience, needs, and preferences are heard and considered throughout the development and approval process

- The FDA uses different channels and methods to gather patient data:
  - PFDD meeting
  - Patient Reported Outcome (PRO) measures
  - Clinical Outcome Assessment (COA)
  - Patient Listening Sessions

Including Patients Perspectives During Discovery and Clinical Phase

➢ Patients Focus Drug Development Meetings

- Public meeting focused on a specific disease
- FDA hears directly from patients, caregivers, and advocates
- Pateints share their experience with the disease, impact on their life, most relevant symptoms, and discuss treatment options
- Helps FDA understand what outcomes are more important to patients
- Informs the design of clinical trials (primary endpoints) and what constitute a meaningful benefits and accepted risk

Including Patients Perspectives During Discovery and Clinial Phase

- **The voice of Patient Report**
  - A summary of the PFDD meeting

- **Patient-Reported Outcome (PRO) measures**
  - Measurement of aspects of patient's health status that comes directly from the patient
  - Data from PRO provide direct evidence of a treatment's benefit from the patient's perspective (pain level, fatigue, ability to perform daily tasks)

- **Clinical Outcome Assessments (COSs)**
  - Broader assessment that includes PRO, observer-reported, clinician-reported, performance outcome

Including Patients Perspectives During the Drug Regulatory Review Process

- **Patient Listening Sessions**
  - Confidential meeting with patient advocacy groups
  - Allows review team to gain deep understanding of patient preferences for risk-benefits trade-off and what patients consider a meaningful clinical benefits

- **Patient Consultant Programs**
  - Patient representative as temporary special government employee on FDA advisory committee

- **Submission of Patient Experience Data by Drug Developers/Sponsors**
  - Drug companies include data gathered from patients in the application to FDA to support their case of approval

Conclusion I

- The drug development endeavor is a complex process:
  - We want **SAFE** drugs, but we want them **FAST**
  - We want **INNOVATIVE** new cures, but we also we want them to be **AFFORDABLE**
  - We want **GLOBAL ACCESS** to breakthrough, but we want a system that **REWARDS THE RISK** of creating them
- The “realistic” goal:
  - Perfect system vs. a more just system

Conclusion II

- **Regulatory Science Supports Drug Development and Promotes collaboration**
  - Provides evidence-based standards to assess safety and efficacy
  - Engage patients and public stakeholders early
  - Support international regulatory harmonization
  - Encourages public-private partnerships
  - Develops real-world evidence capabilities
  - Creates new development tools and approaches
  - Enhances transparency and communication

Спасибо

Obrigado

Cảm ơn

Merci

Kiitos

شکریہ

Bedankt

Thank you

Grazie

Gracias

Terima kasih

Dank u wel

Takk

ありがとう

감사합니다

شكراً

Teşekkür ederim

Mahalo