Precision Oncology – Early Development in view of New Regulations

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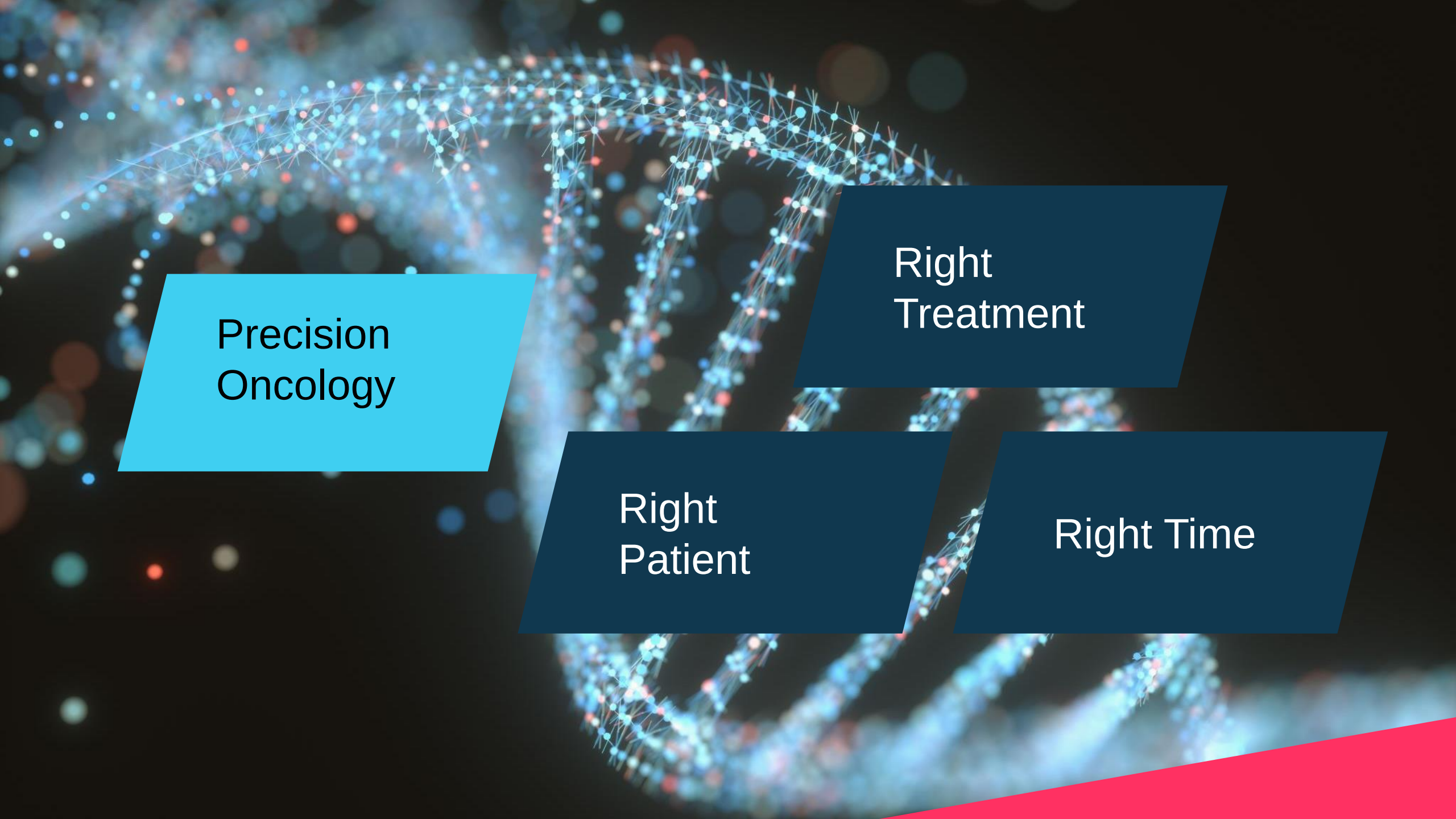
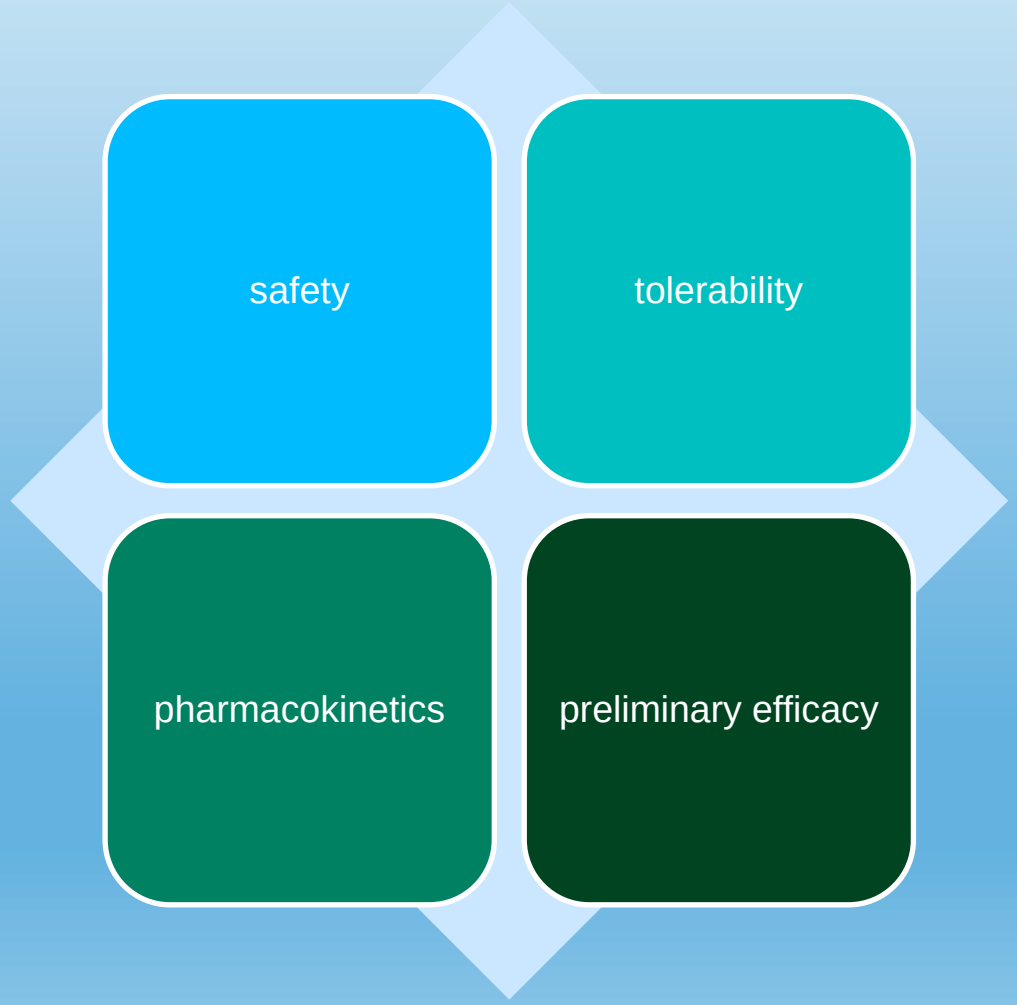
CDDF Annual Meeting
February 2025


Precision Oncology
Right Treatment
Right Patient
Right Time

Early Phase Oncology Drug Development Studies



- Single arm trials
- All-comers vs biomarker-selected
- Biomarker exploratory analyses
- Larger portion of portfolio
- Seamless phase transitions

United States

Overview of FDA's Final Rule on Laboratory Developed Tests

https://www.federalregister.gov/public-inspection/2024-08935/medical-devices-laboratory-developed-tests

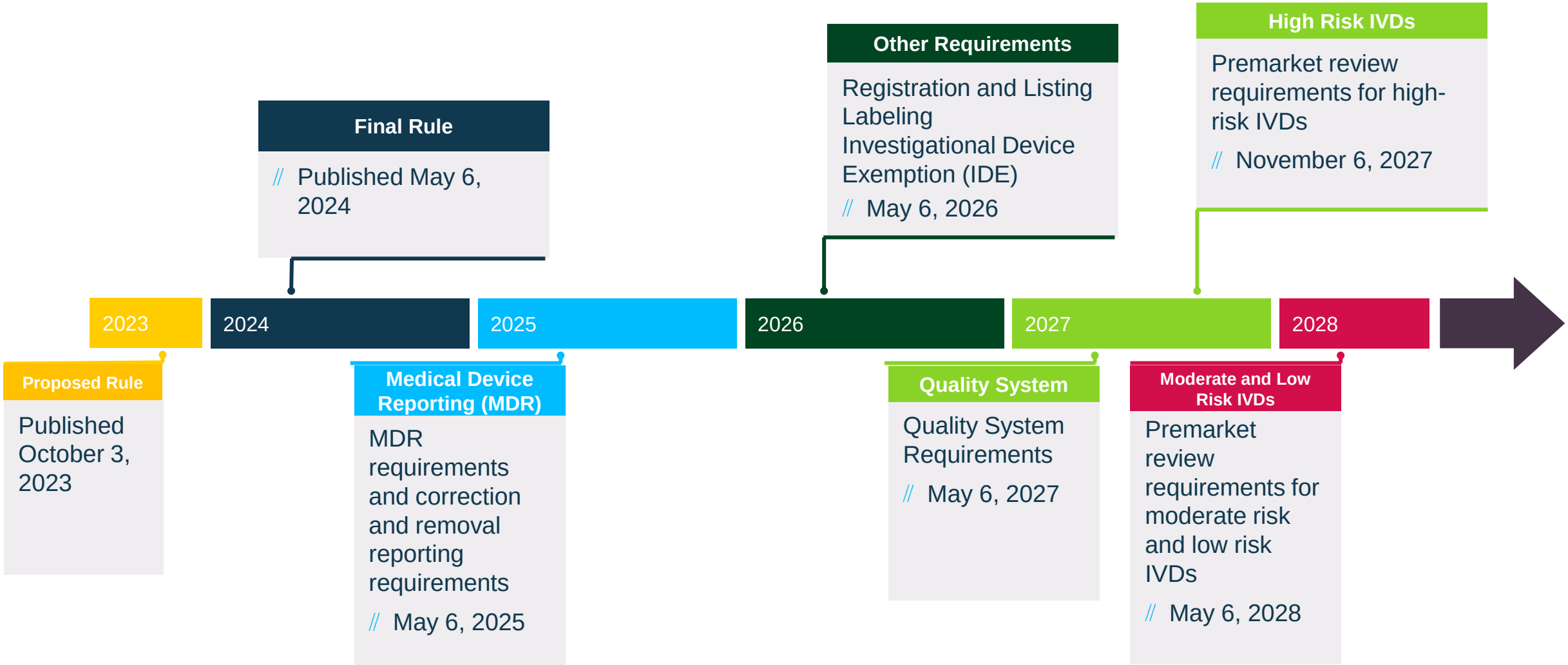
Amends the definition of "*in vitro* diagnostic products" to make explicit that IVDs manufactured by laboratories are devices under the FD&C Act.

Describes the need for the rule as well as the legal basis for the final amendment, summarizes and addresses public comments.

Proposes a phase out of its general enforcement discretion approach for laboratory developed tests (LDTs).

Timeline to Full Implementation

FDA Final Rule - Laboratory Developed Tests

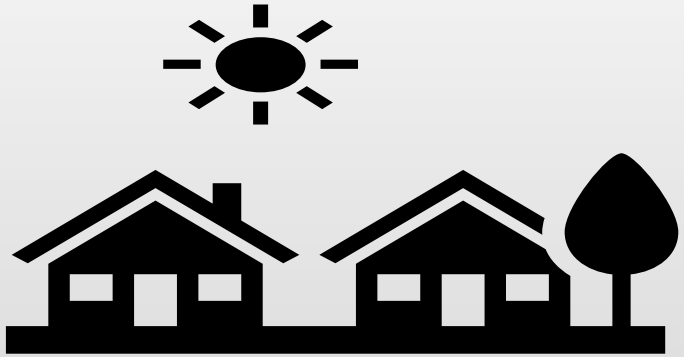


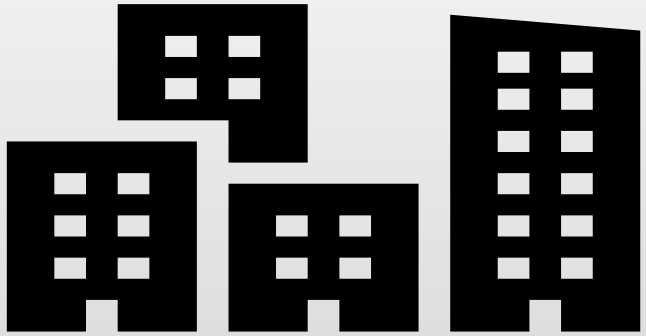
Enforcement Discretion (ED) under Final Rule

	MDRs, Complaints, Corrections (Stage 1)	Registration & Listing, Labeling, IDEs (Stage 2)	Quality System (Stage 3)	Pre-Market Review (Stage 4&5)
Currently marketed LDTs[1]	**Required**	**Required**	**ED[3]**	**ED**
LDTs for unmet needs[2]	Required	Required	ED[3]	ED
LDTs Approved by the NYS CLEP	Required	Required	Required	ED

[1]Prior to May 6, 2024
[2] Used in an integrated healthcare system
[3] 21 CFR Part 820 Subpart M- Records still applies

Biomarker Assays Used for Enrollment





Use of Local Assays for Enrollment

Availability of local tests for enrollment into drug clinical trials may be impacted

Central testing may be needed as an alternative to enrolling using local test results

Use of Central Assays for Enrollment

Already subject to IDE regulations

Early phase trials more heavily impacted since IDEs less common for central assays in this setting

Use of Biomarkers - Exploratory vs Key Objectives

LDT Final Rule – Status quo

FDA Draft Guidance on Considerations for Including Tissue Biopsies in Clinical Trials (Jan 2025)

- Required biopsies must be justified by the necessity of the data they provide (e.g., eligibility criteria, primary/secondary endpoints).
- Optional biopsies should not impose undue burden or risk on participants.
- Biopsies solely for exploratory endpoints or future research should be optional.

Operational Diagnostic Testing

Avoiding disruption of drug clinical trial operations under LDT Final Rule

Preventing disruption of drug clinical trial operations under the LDT Final Rule:

// Patients should have access to FDA registered and listed tests from CLIA certified laboratories that are used in accordance with their labeling

// FDA registered and listed tests from CLIA certified laboratories used in accordance with their labeling for routine *non-investigational* IVD testing.

FDA to Down-classify CDx Devices

CDRH Announced Intent to Initiate the Reclassification Process for Most High Risk IVDs in January 2024

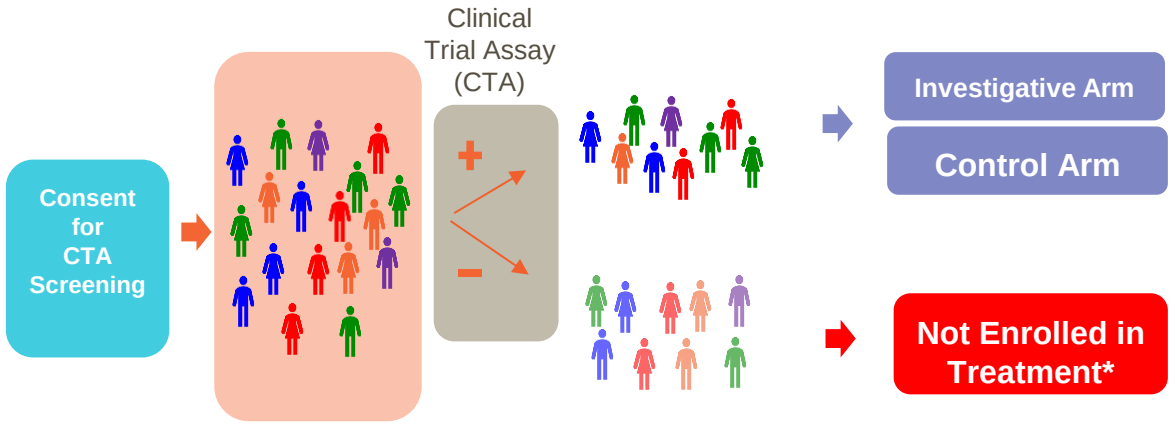
https://www.fda.gov/medical-devices/medical-devices-news-and-events/cdrh-announces-intent-initiate-reclassification-process-most-high-risk-ivds

- ❑ Substantial Equivalence vs Safety and Effectiveness
- ❑ Quality System Documentation and Inspections
- ❑ Timelines
- ❑ Modular Submissions
- ❑ Conditions of Approval/Authorization (CoA)

Substantial Equivalence for CDx Submissions

Will data requirements change for CDx submissions?

		Authorized CDx Assay		
		Positive	Negative	Total
Investigative CDx Assay	Positive	A	B	A+B
	Negative	C	D	C+D
	Total	A+C	B+D	A+B+C+D
Positive Percent Agreement (PPA)		A/(A+C)		
Negative Percent Agreement (NPA)		D / (B +D)		
Positive Predictive Value		A / (A + B)		
Negative Predictive Value		D / (C+D)		



Substantial Equivalence

Evaluates whether a new assay is concordant to an authorized CDx (same analysis concept as “follow-on” CDx). More reliance on procured specimens.

OR

Substantial Equivalence

Evaluates whether a new assay has similar clinical performance to a previously authorized CDx (similar analysis to safety and effectiveness). More reliance on drug clinical trial specimens.

*Not ideal for CDx evaluation, but common design element of pivotal Rx/CDx trials with strong link of biomarker to therapy target

LDT Final Rule and IVD Reclassification Impacts

United States

Availability of local tests for enrollment into drug clinical trials may be impacted by LDT Final Rule.

Applicability of IDE regulations for investigational LDTs have not changed, but potential for greater need for early phase trials under LDT Final rule.

Non-investigational (on-label) use of FDA registered and listed assays from CLIA certified laboratories should be allowed in drug clinical trials in cases where FDA-cleared or approved assays are not available to avoid disruptions.

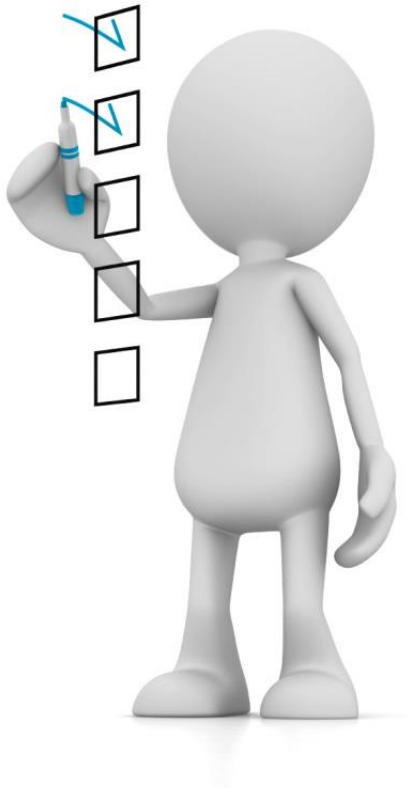
Down-classification of CDx devices from Class III to Class II should improve US CDx development timelines and lower submission costs.

European Union

Key IVDR Requirements

In Vitro Diagnostic Regulation (EU) 2017/746, effective May 2022

- Regulatory Classification (Article 47 & Annex VIII)
- Performance Evaluation and Clinical Evidence (Article 56 & Annex XIII)
- Labeling and Instructions for Use (Annex I Chapter III)
- Conformity Assessment (Article 48, Annex IX and XI)
- Quality Management System (Article 10, Annex I, Annex IX)
- Post-Market Surveillance (Article 78 to 83 & Annex III)
- Performance Study Notification/Application (Article 57, 58 & 66 & Annex XIV)



IVDR Requirements and Early Phase Drug Clinical Trials

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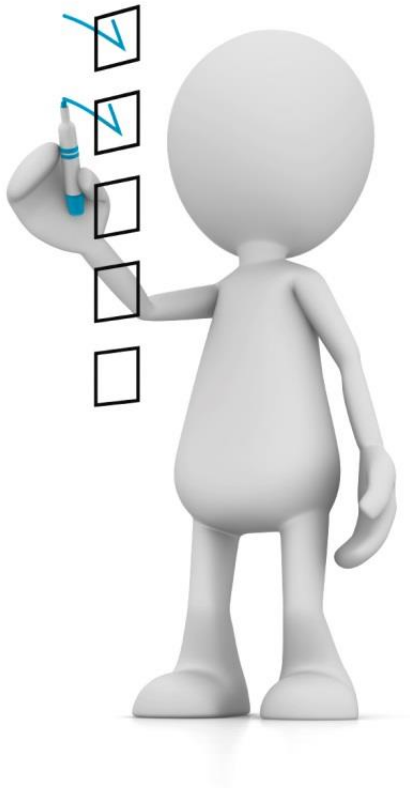
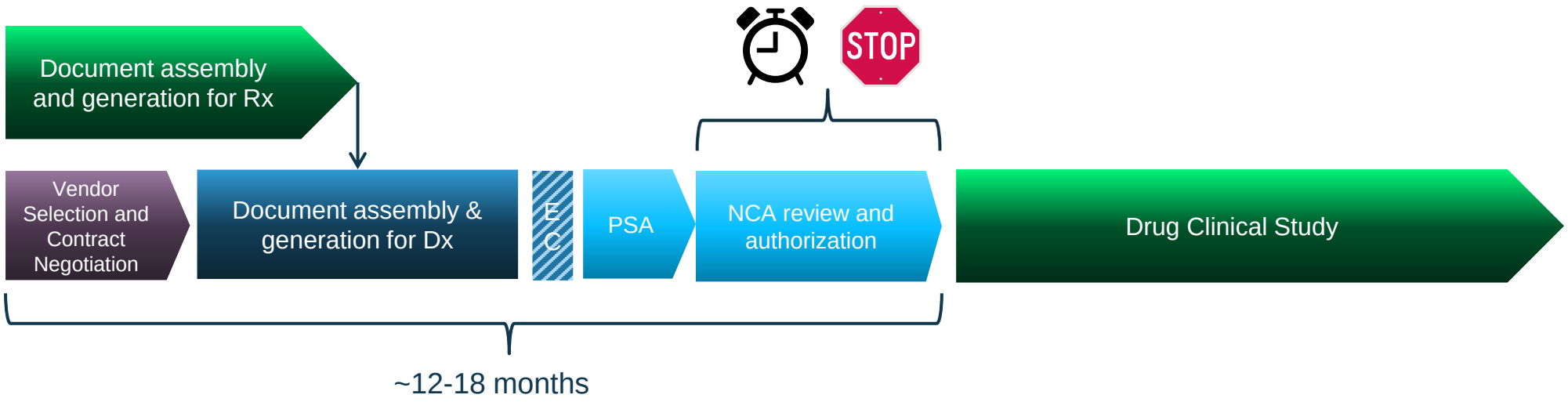
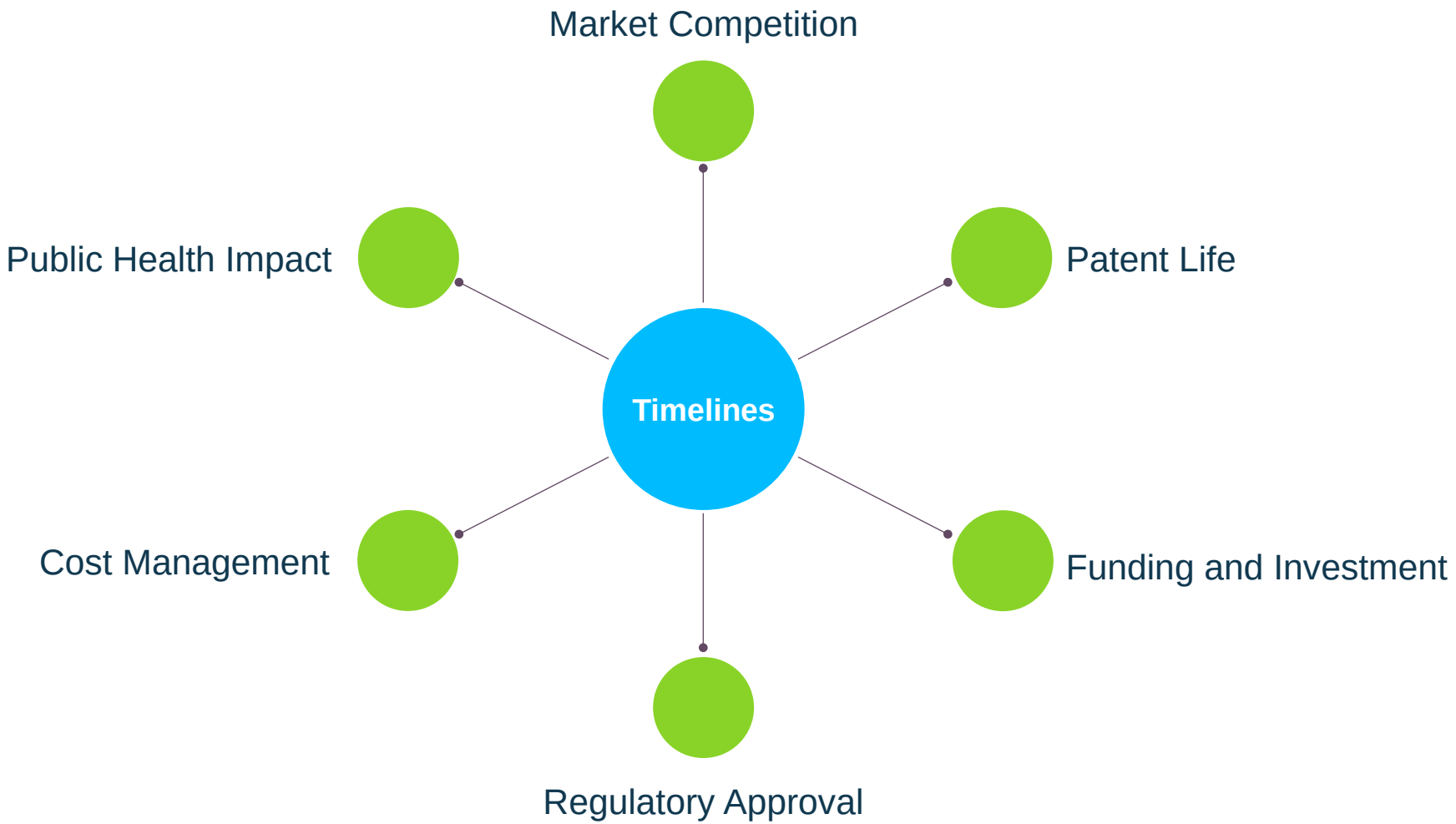


Performance Study Application – Timeline Impact

Prospective Selection with Biomarker Assay into Drug Clinical Trial

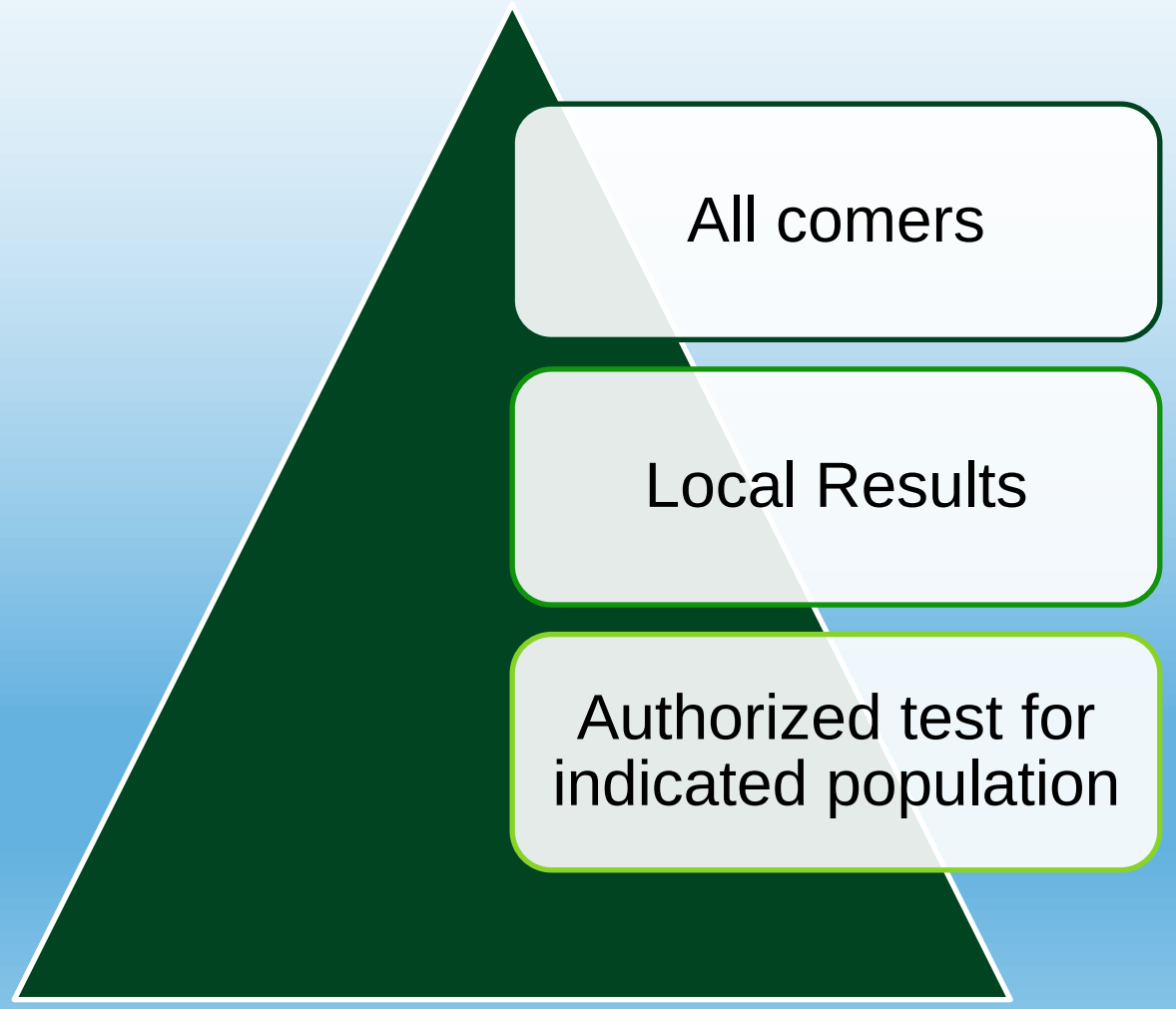


Timelines for Therapeutic Trials are Crucial



Initiating Early Phase Precision Medicine Trials

Timeline Sensitive Options



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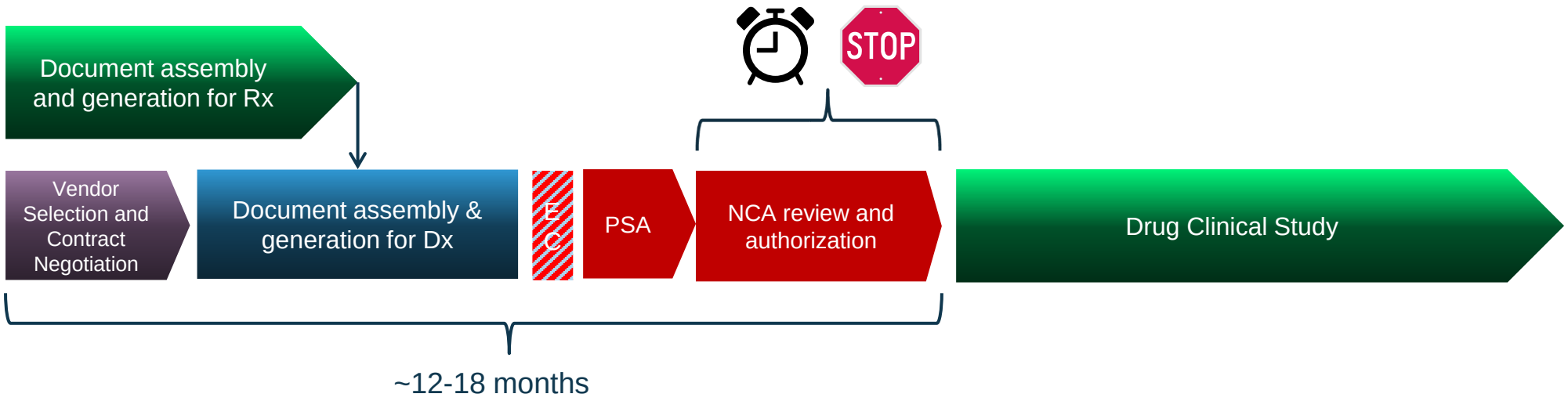
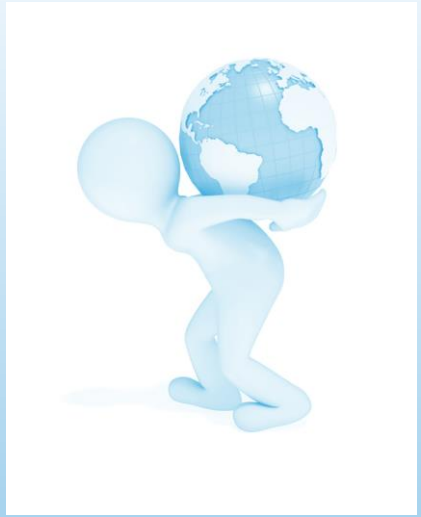
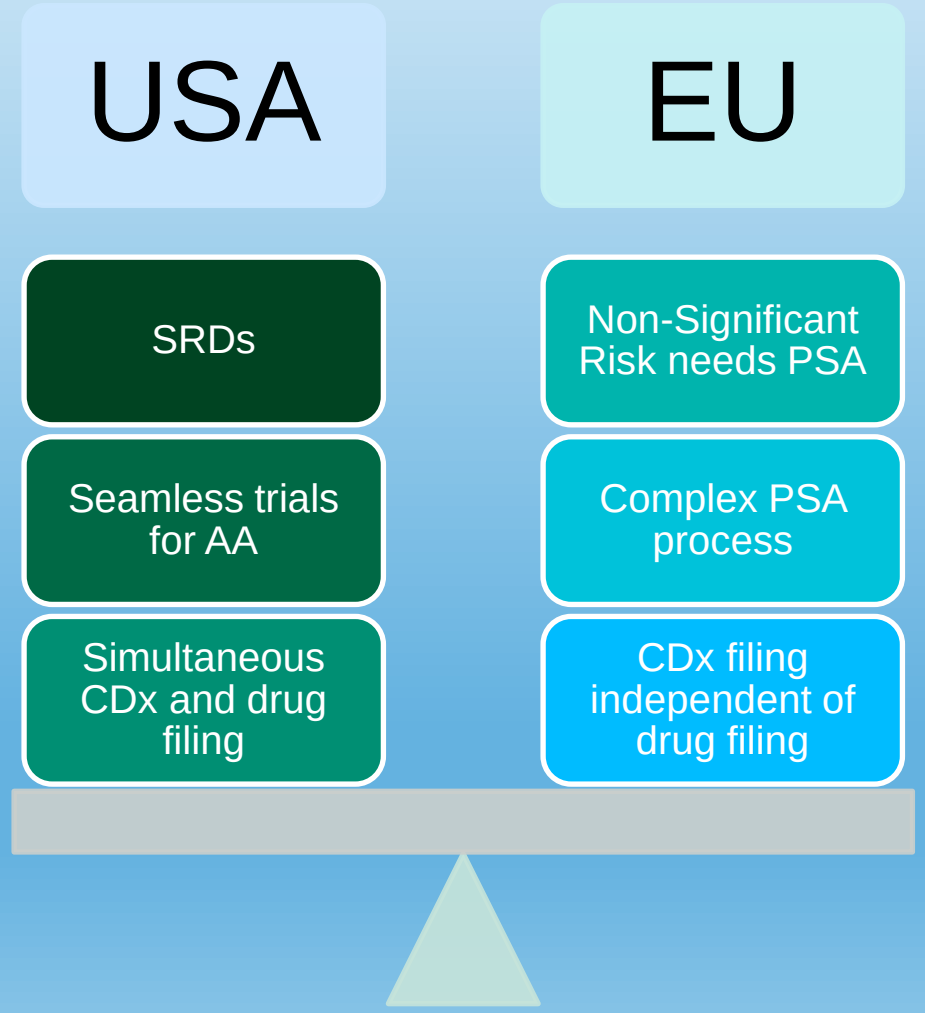


- Study Risk Determination
- No defined window from submission to start of trial
- No centralized pre-submission/assessment process

Early Phase Oncology Drug Development Studies





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- **Larger portion of portfolio**
- **Seamless phase transitions**

Impacts to Early Phase Precision Oncology

- Delays in clinical trial initiation due to new regulations impact risk/benefit profile of precision medicine programs.
- Pragmatic approaches are needed regarding patient selection into early phase clinical trials
- Alignment of IVDR requirements and streamlining of submissions across member states
- Use of a CE-marked assays within their analytical intended purpose
- Allowance for local and in house testing for early phase clinical trials.

Thank You!

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