Global Companion Diagnostic (CDx) Registration: Clinical Evidence and Regulatory Pathways

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Characteristics of Companion Diagnostics

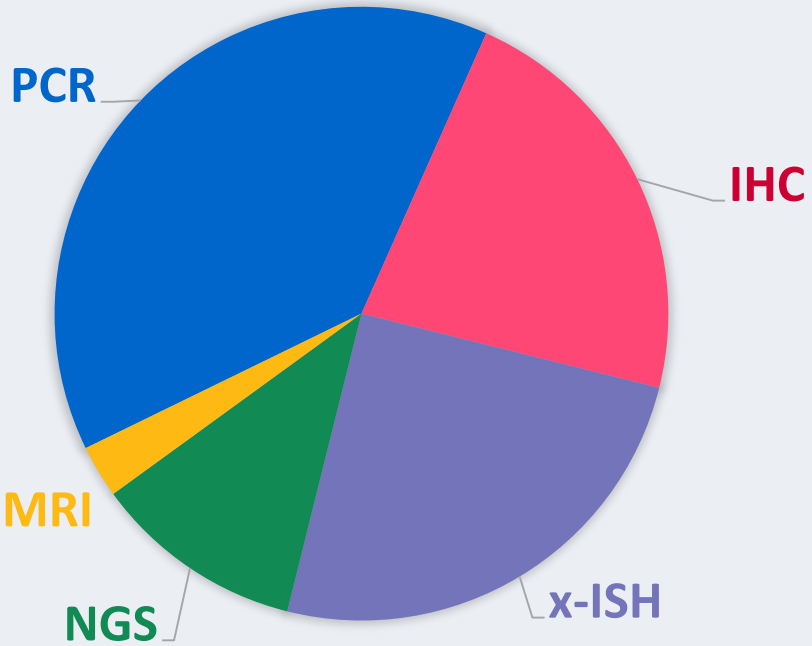
Summarized from 38 US-approved CDx

35 Oncology | 3 Other disease

25 One drug | 13 Multi-drug

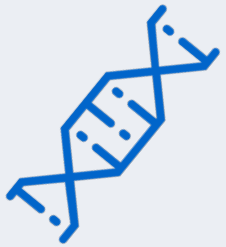
BIOMARKERS

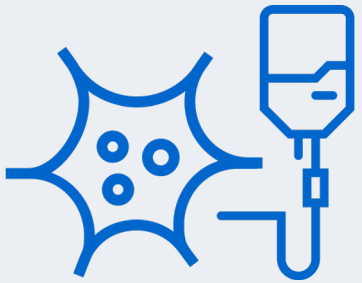
TECHNOLOGY



Data source: FDA list of Approved CDx, last updated Oct 23, 2019 https://www.fda.gov/medical-devices/vitro-diagnostics/list-cleared-or-approved-companion-diagnostic-devices-vitro-and-imaging-tools

Shape the regulatory landscape to ensure Companion Diagnostics (CDx) reach patients





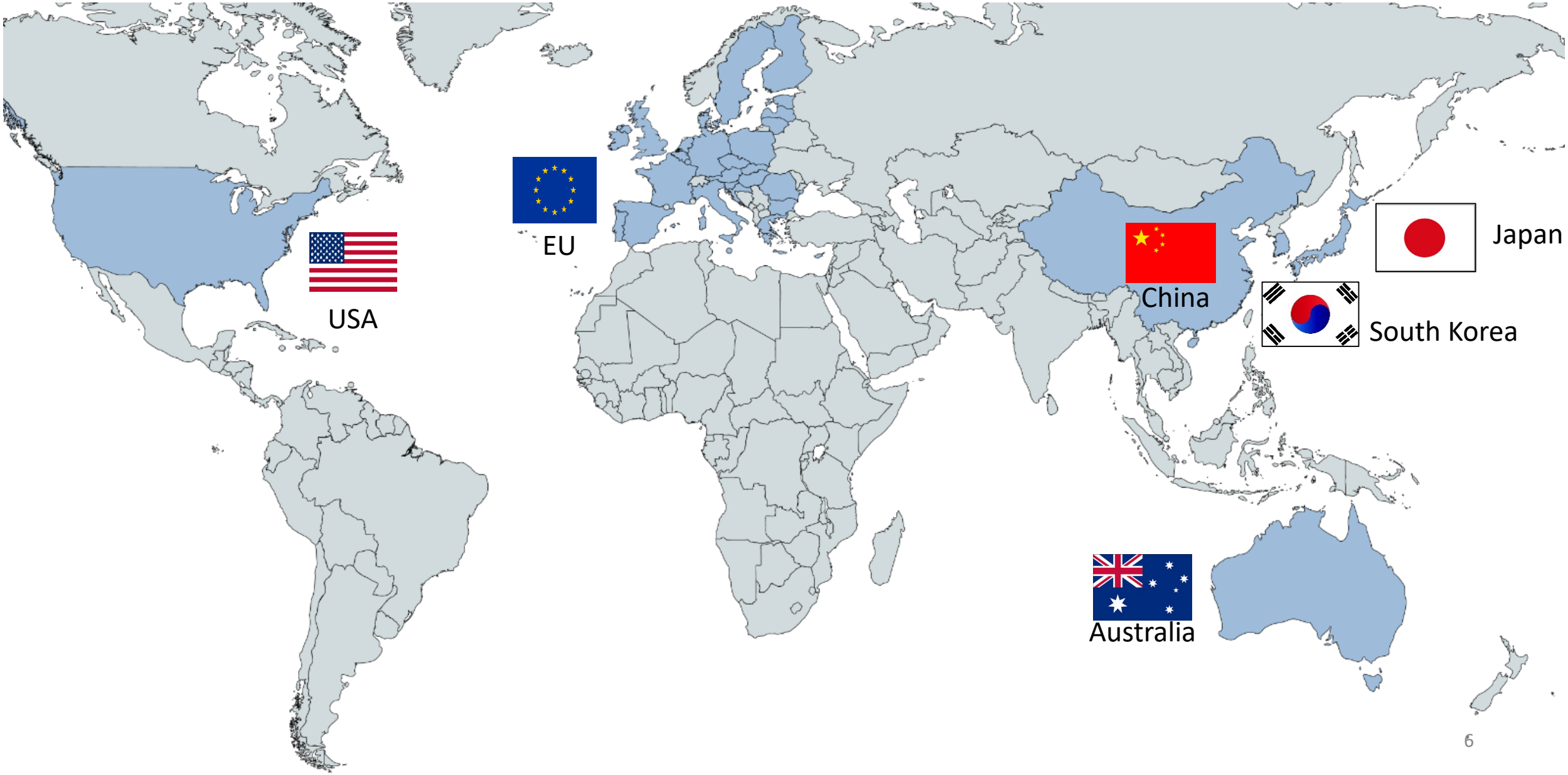
- Definition & Labeling
- Clinical Evidence
- Registration Pathway

Save Lives

Global Landscape:
A brief overview

…trend towards increasing regulation

Countries/ Regions with specific CDx Regulations or Guidance



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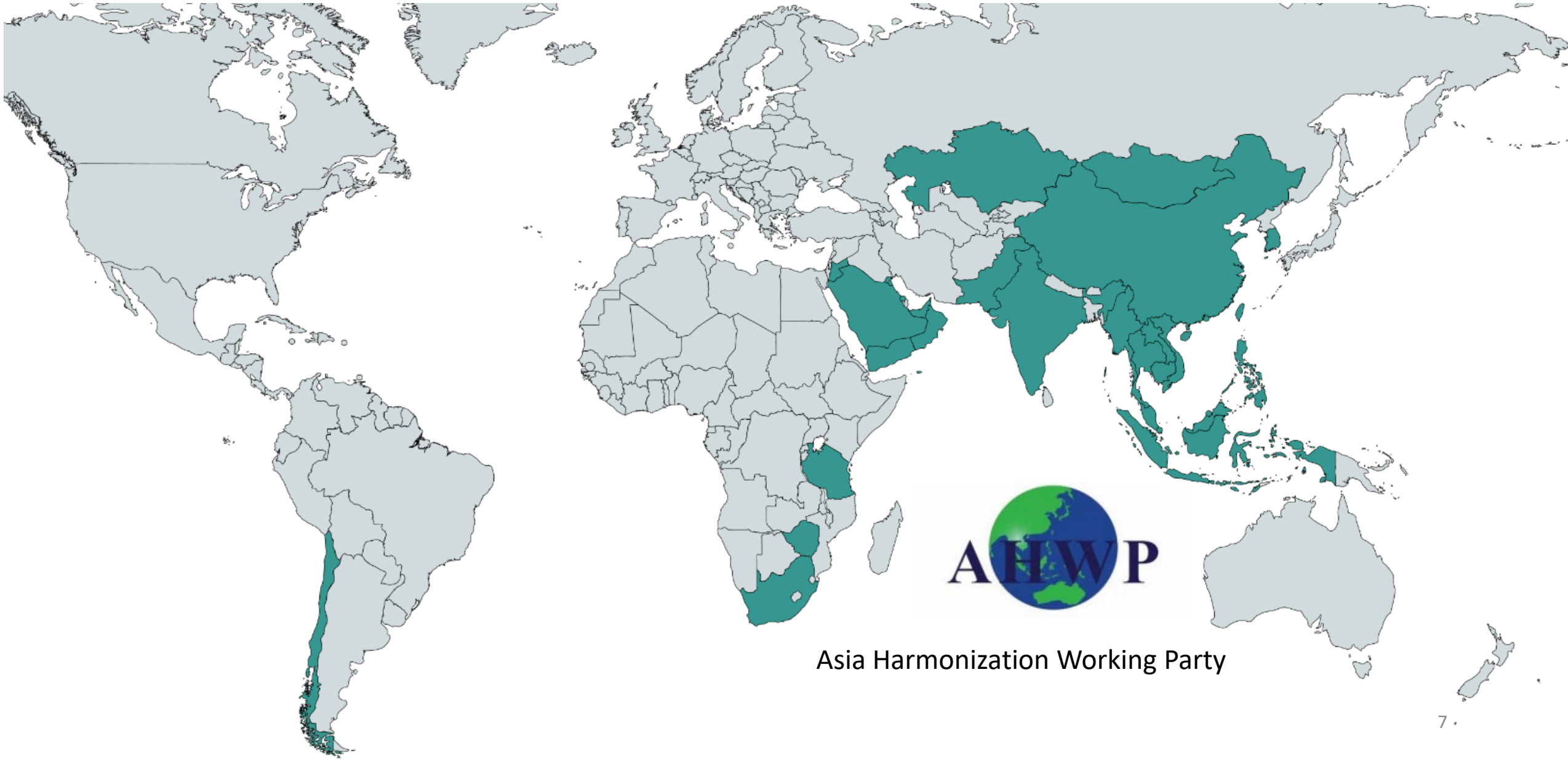


Asia Harmonization Working Party

CDx Definition:

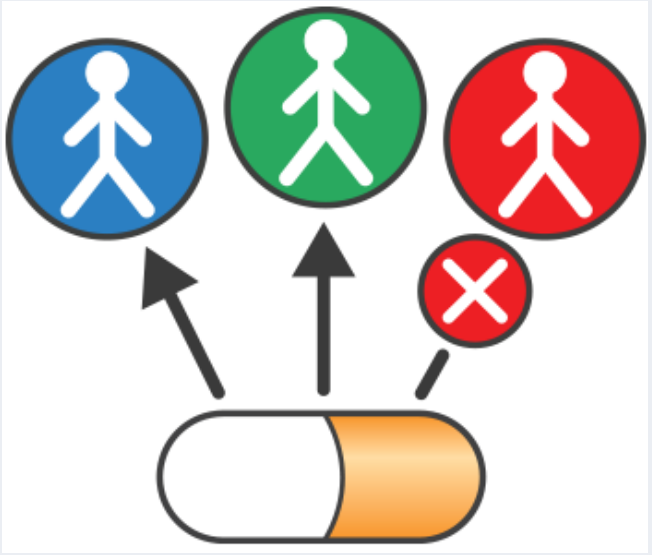
Essential for the use of corresponding drug

…and reflected in the labelling of both products

CDx Definition

Basic Elements

Companion Diagnostic (CDx) : an in vitro diagnostic device (IVD) that is **required** for the proper use of a specific targeted drug



- **Select patients who are eligible for treatment**
- **Predict benefit from treatment**
- **Identify patients at increased risk for serious adverse events**

Not CDx:

- Therapeutic drug monitoring
- Viral load testing
- Coagulation testing
- Complementary Diagnostics

CDx Definition: essential for use of corresponding drug

AHWP

"Companion In Vitro Diagnostic Medical Device ' means an in vitro diagnostics medical device which is essential for the safe and effective use of a corresponding therapeutic product to:

a. identify, before and/or during treatment, patients who are most likely to benefit from the corresponding therapeutic product; or

b. identify, before and/or during treatment, patients likely to be at increased risk of serious adverse reactions as a result of treatment with the corresponding therapeutic product.

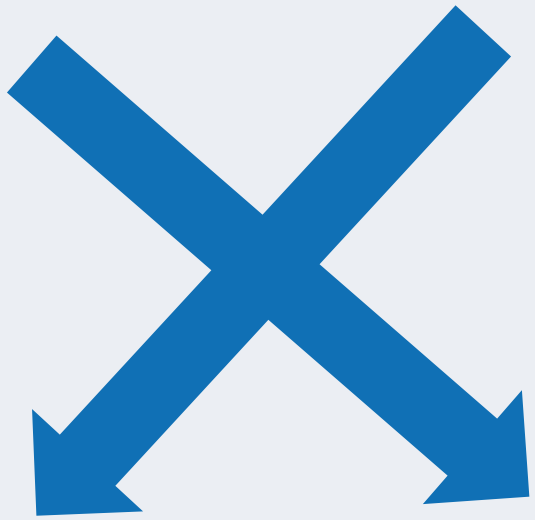
from AHWP/WG2/F001:2017 "Proposed Guidance for Additional Considerations to Support Conformity Assessment of Companion In Vitro Diagnostic Medical Devices" 4 Sept 2017

CDx Labeling: CDx status in both drug and device label

Crosslabeling

CDx Label

- Intended use statement describes use with specific drug or class of drugs
- Clinical Performance section summarizes CDx performance in terms of drug



Targeted Drug label

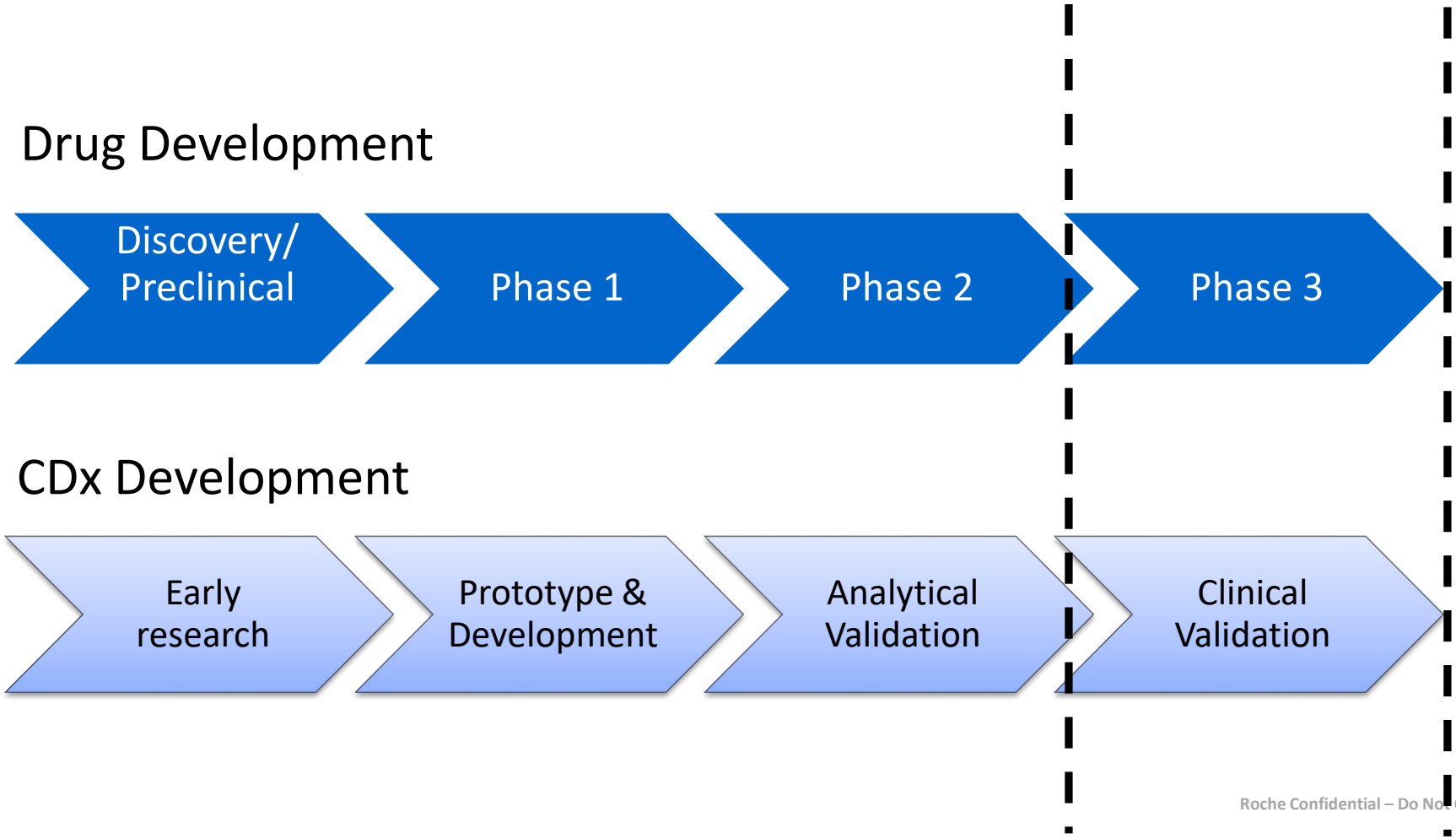
- Reflects need for biomarker assessment with a registered/ validated assay
- Specific assay name can appear in Clinical Performance section

CDx Clinical Evidence:
Use of CDx with the drug must be supported by valid clinical evidence

…alternative evidence sources should be considered

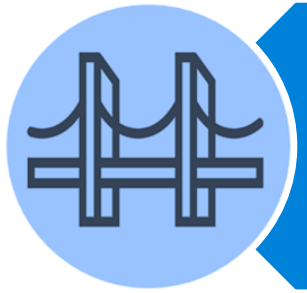
CDx must be supported with valid clinical evidence

Ideal option: use of the CDx in the registrational drug trial



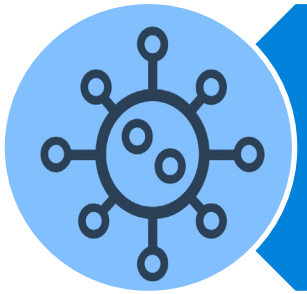
CDx: valid clinical evidence from alternative sources

International principles urge consideration of clinical trial alternatives



Concordance studies

Overseas clinical data



Real World Evidence

CDx: valid clinical evidence from alternative sources

Concordance studies with specialized statistical analysis

Bridging study

When

- Final assay not ready in time for trial
- Follow-on CDx

How

- Concordance to assay used in study
- Statistical analysis to show utility with drug

Analysis

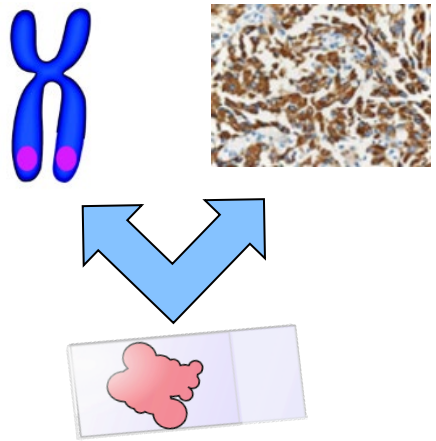
- Remeasure trial samples: drug outcome available
- No trial samples: published statistical method

Meijuan Li (2016) Statistical Methods for Clinical Validation of Follow-On Companion Diagnostic Devices via an External Concordance Study, Statistics in Biopharmaceutical Research, 8:3, 355-363, DOI: 10.1080/19466315.2016.1202859

CDx: valid clinical evidence from alternative sources

Bridging studies can help drug reach patients faster: ALK story

2014: Drug approved



New TKI drug approved – requiring 2 CDx.

Sole CDx assay submission, supported with bridging studies, was denied

New clinical trial required

A new clinical trial was required and began in 2014.

Approvals elsewhere

Drug approved with sole CDx in other jurisdictions as early as 2015. Bridging studies used.

2019: CDx approved

Sole CDx approved 5 years after drug

CDx: valid clinical evidence from alternative sources

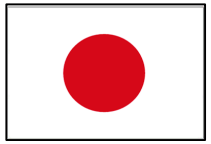
Acceptance of overseas clinical data reduces duplicative trials

Overseas Data Allowed

- Appropriate human subject protection
- Scientifically valid study design
- No known ethnic differences


China


USA


Japan


EU (IVDR)


Brazil


Canada


South Korea

CDx: valid clinical evidence from alternative sources

Overseas clinical data success story : EGFR

Original requirement

Clinical trial in China with 1000 patients specimens

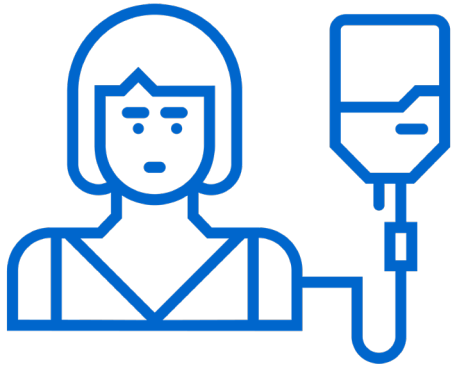
2018 policy change

2018: China allows data from foreign clinical trials

Overseas data provided

Aggregate global clinical trial data was submitted

Patients get access sooner



CDx approval gained ~2.5 years earlier

CDx: valid clinical evidence from alternative sources

Acceptance of overseas clinical data is implicit in reliance and recognition pathways

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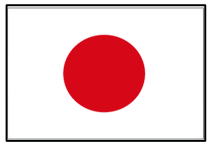
Japan


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Reliance/ Recognition Pathways

- Reference country approval leveraged
- Immediate approval or abridged review
- Conserves reviewer resources

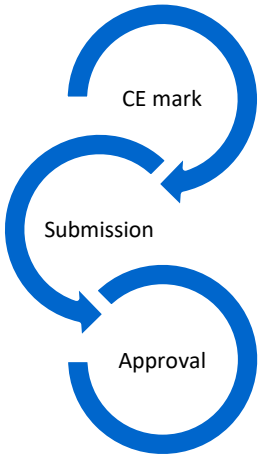

Australia


Singapore

CDx: valid clinical evidence from alternative sources

Reliance and recognition success story : PDL1

Original process



October 2018: Australia expands list of comparable overseas regulators to include US FDA

2018 policy change

October 2018: Australia expands list of comparable overseas regulators to include US FDA

FDA data provided

Data from March 2019 PD L1 triple negative breast cancer CDx approval submitted

Rapid approval

TGA approval via abridged process in only **25 days**

CDx: valid clinical evidence from alternative sources

***Real World Evidence* can be used in regulatory decision-making**

Relevant

to the regulatory question at hand

Reliable

rigorous data management and analysis processes to ensure quality

Approval Year	Product	RWE source
2017	Tumor Profiling test	Public clinical database Published results
2017	Oncology Panel	Routine clinical use data
2018	Blood glucose meter	Lab Information System retrospective data
TBD	CDx Assay	Aggregated Electronic Health Records

CDx Review Pathways:
Must be predictable and efficient

…collaboration and communication are essential

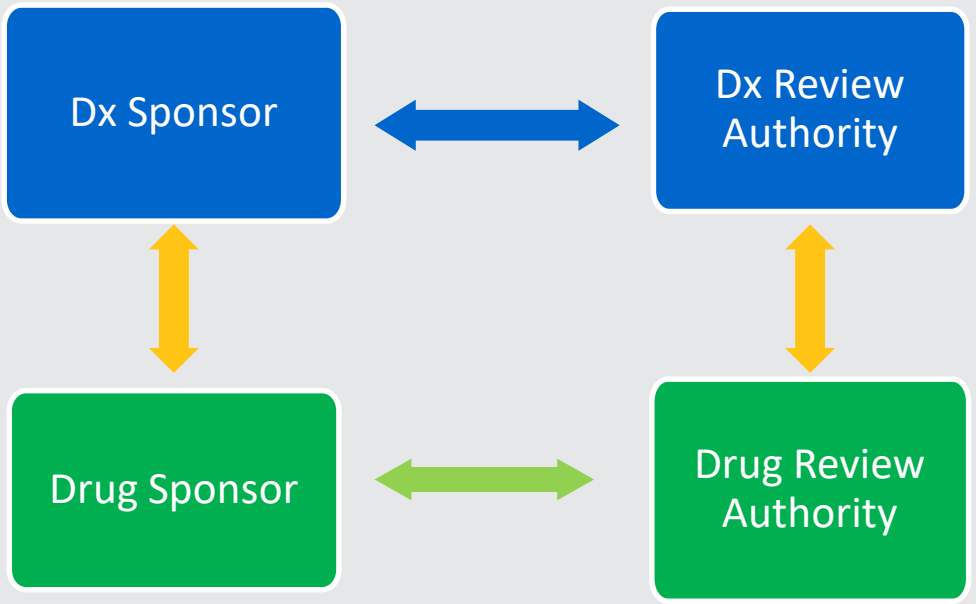
CDx review pathways must be predictable and efficient

Two models: Cooperative and Separate

Cooperative Review

Goal: simultaneous approval of CDx and drug

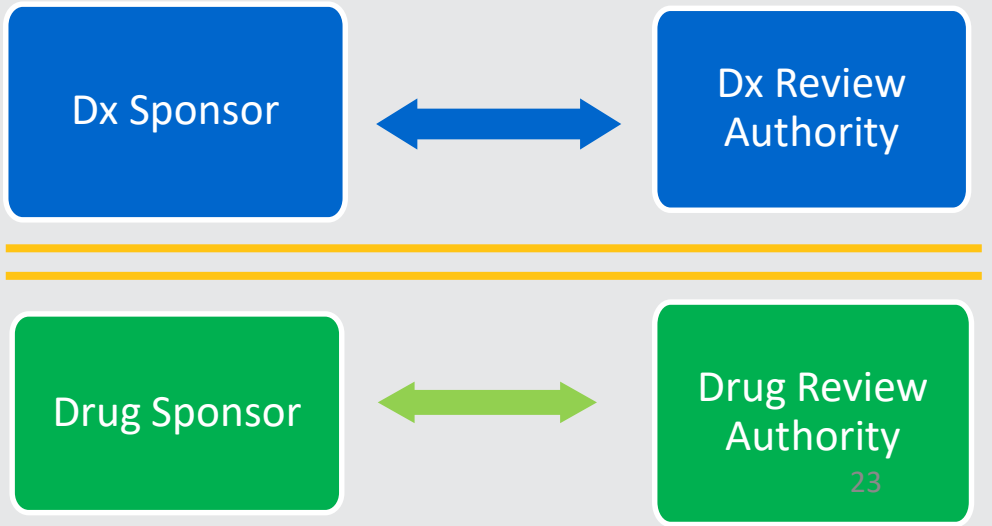
Requires process for interaction among health authority review centers and sponsors



Separate Review

CDx is reviewed like any other IVD

Efficient, especially if local requirements are minimized



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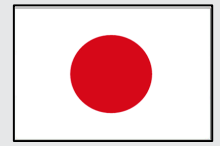

Japan

EU (IVDR)

South Korea

China

Separate Review

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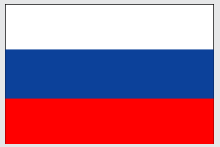
Brazil

Canada

EU (IVDD)

Singapore

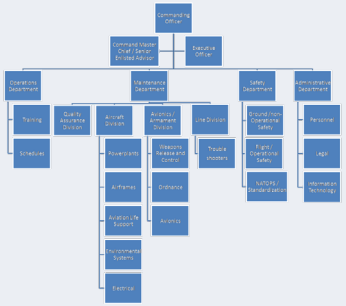


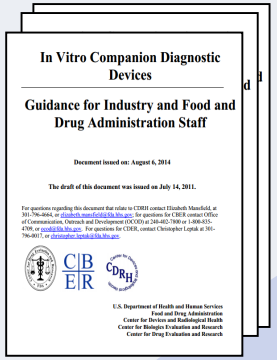
Russia

CDx review pathways must be predictable and efficient

Evolution of US CDx regulatory pathway

Infrastructure changes

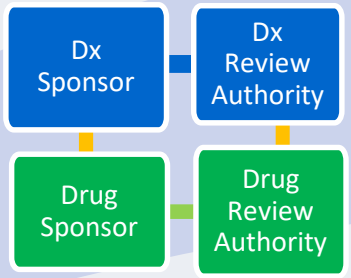




Guidances

1998
Herceptest -
Herceptin

2011
BRAF -
Zelboraf



4-sided Project Meetings

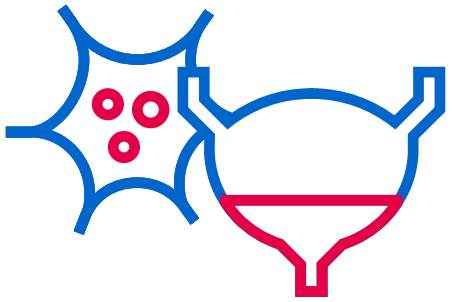
2019: **38** Approved CDx

Public Stakeholder Workshops

CDx review pathways must be predictable and efficient

Communication is essential for patient safety: PDL-1 story

Science evolves

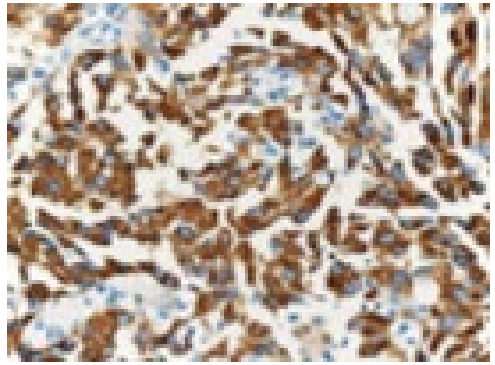


Interim trial results showed drug only works for bladder cancer in patients with PDL-1

Drug authorities react

The labelling of the drug was updated to reflect the need for a PDL-1 CDx in Bladder Cancer

CDx indication extension



Corresponding PDL-1 CDx registrations were performed.

2 were successful.

1 CDx submission denied

Traditional package of clinical data was not available

No discussion between Device and Drug Reviewer

CDx review pathways must be predictable and efficient

Collaborating on interaction pathway in the EU

Diagnostics and Pharma stakeholders work together

- Assessment of CDx under IVDR
  - Notified Body – EMA interactions
- Use of CDx in Pharma clinical trials
- Labelling of CDx and Drugs

efpia
European Federation of Pharmaceutical Industries and Associations

MedTech Europe
from diagnosis to cure

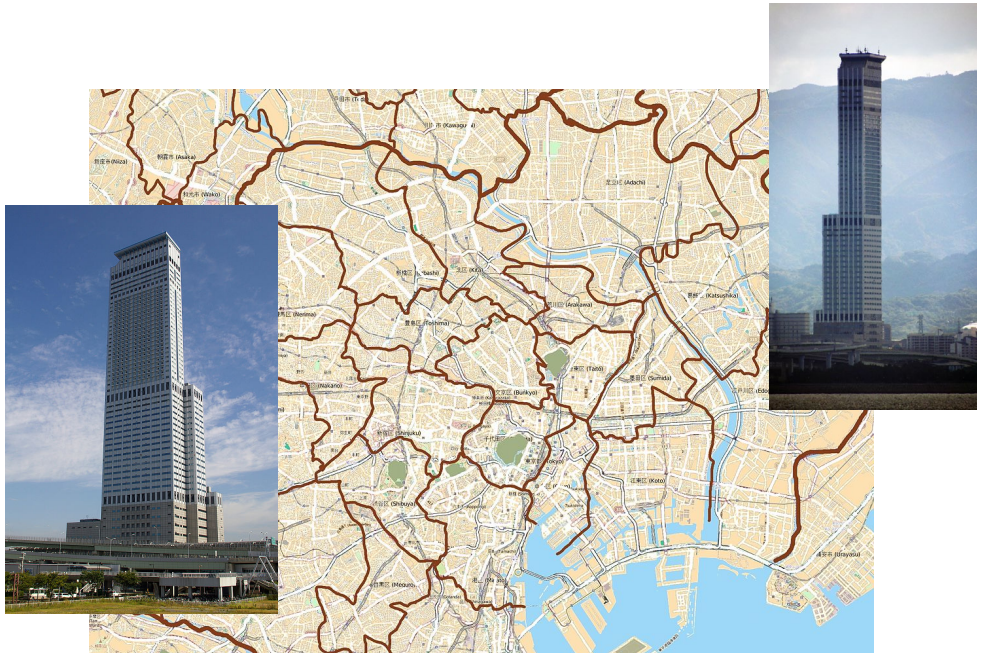
CDx review pathways must be predictable and efficient

Cooperative and Separate – which is better?

Cooperative Review recommended

Infrastructure, resources, and process for cooperative interaction

First-time approval of new drug with companion diagnostic



Separate Review recommended

Reliance and recognition pathway

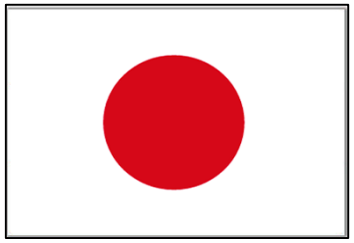
No established interaction process

CDx review pathways must be predictable and efficient

With breakthrough pathways, CDx reach patients sooner

Special Innovative Review Process

Breakthrough Device Pathway



Sakigake Designation Pathway

Special Act for Innovative Devices

Breakthrough Program Features

Increased dialog with authority

Accelerated process

Shape the regulatory landscape to ensure Companion Diagnostics (CDx) reach patients

CDx Basics

- Essential for use of drug
- Crosslabeling CDx and drug

Clinical Evidence

- Concordance studies
- Overseas evidence, reliance
- Real World Evidence

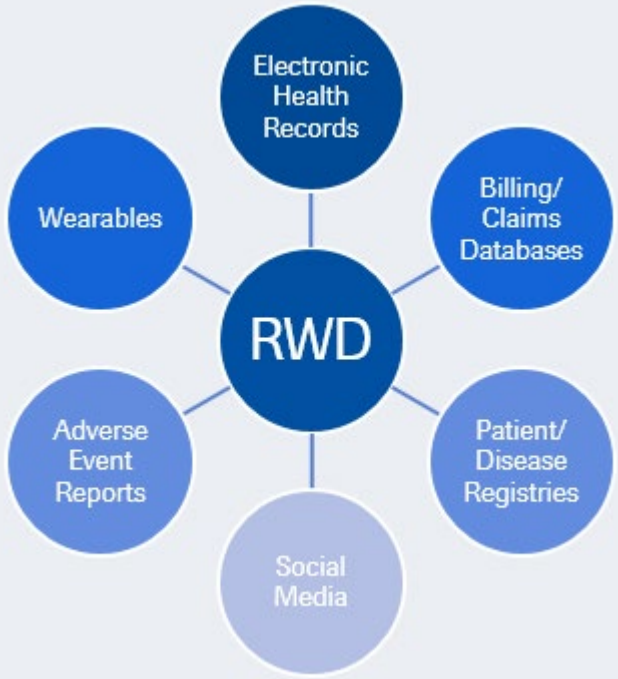
Review Pathways

- Cooperative or separate
- Communication is key
- Breakthrough Pathways

Doing now what patients need next

CDx: valid clinical evidence from alternative sources

Technological advances create opportunities for Real World Evidence



Aggregate

Analyze

Real World Evidence (RWE)

Clinical evidence regarding the usage and potential benefits or risks of a medical product **derived from analysis** of RWD

FDA Guidance Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices Aug 2017