BBS Basler Biometrics Section Seminar on Synthetic Controls

RWD/RWE Global Regulatory Overview

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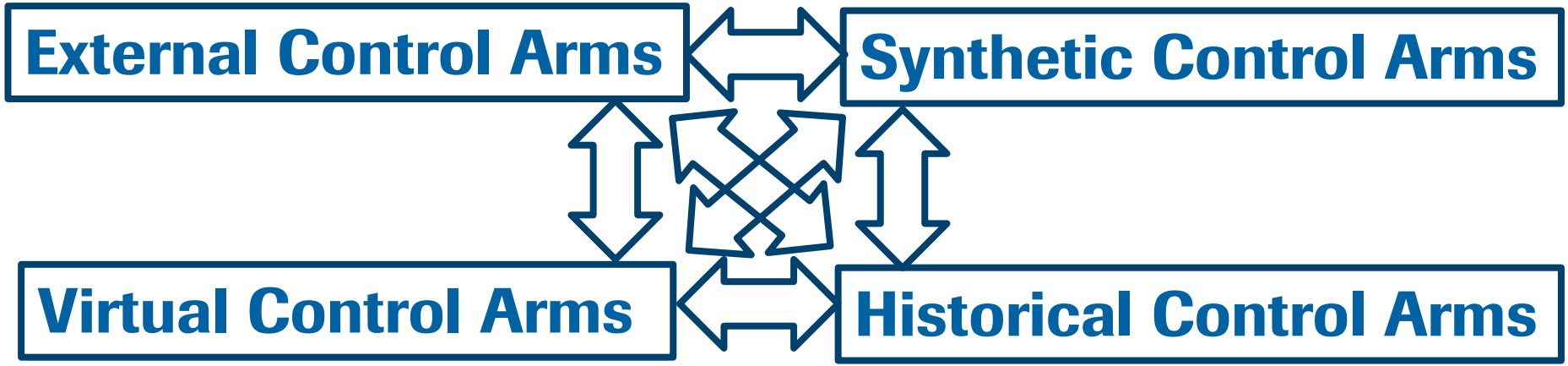
International Regulatory Policy Lead for RWD/RWE
Hoffmann-La Roche, Basel

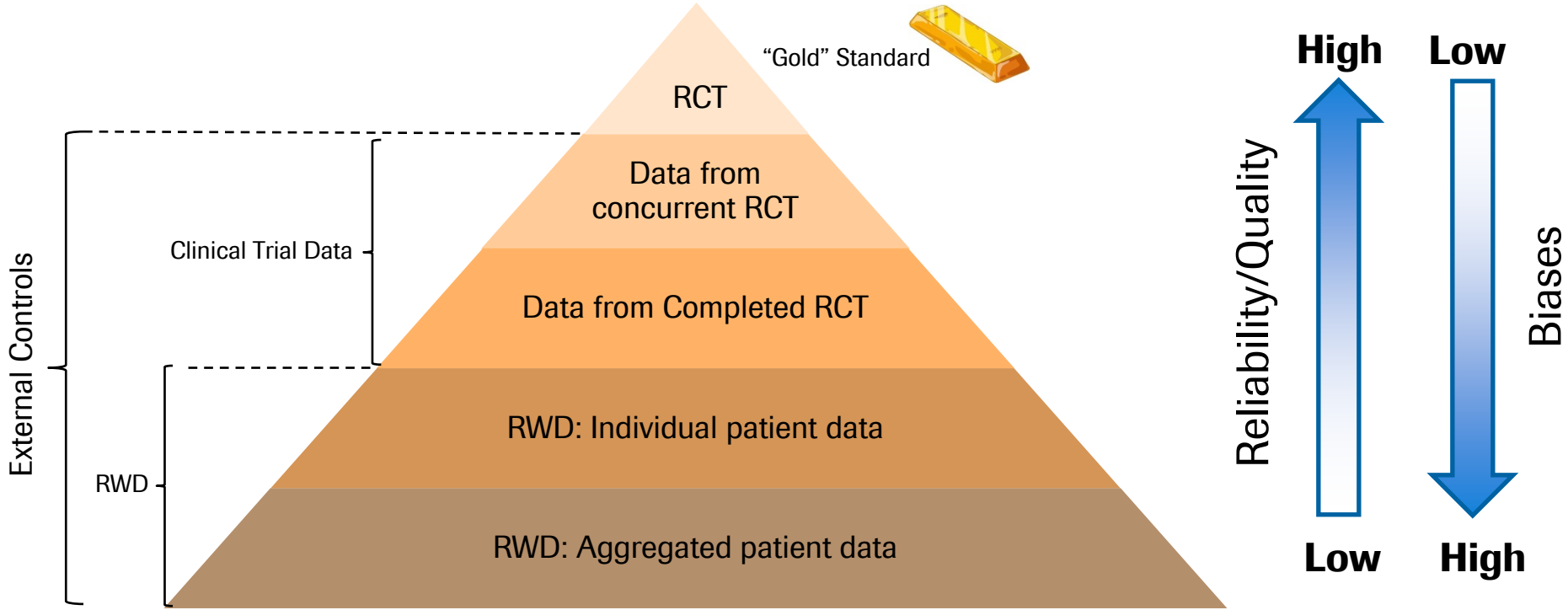
Lets Start with Terminology



- Terms used Interchangeably
- No universally agreed terminology exists
- Seems “External Control” is preferred term

Data used for External Controls

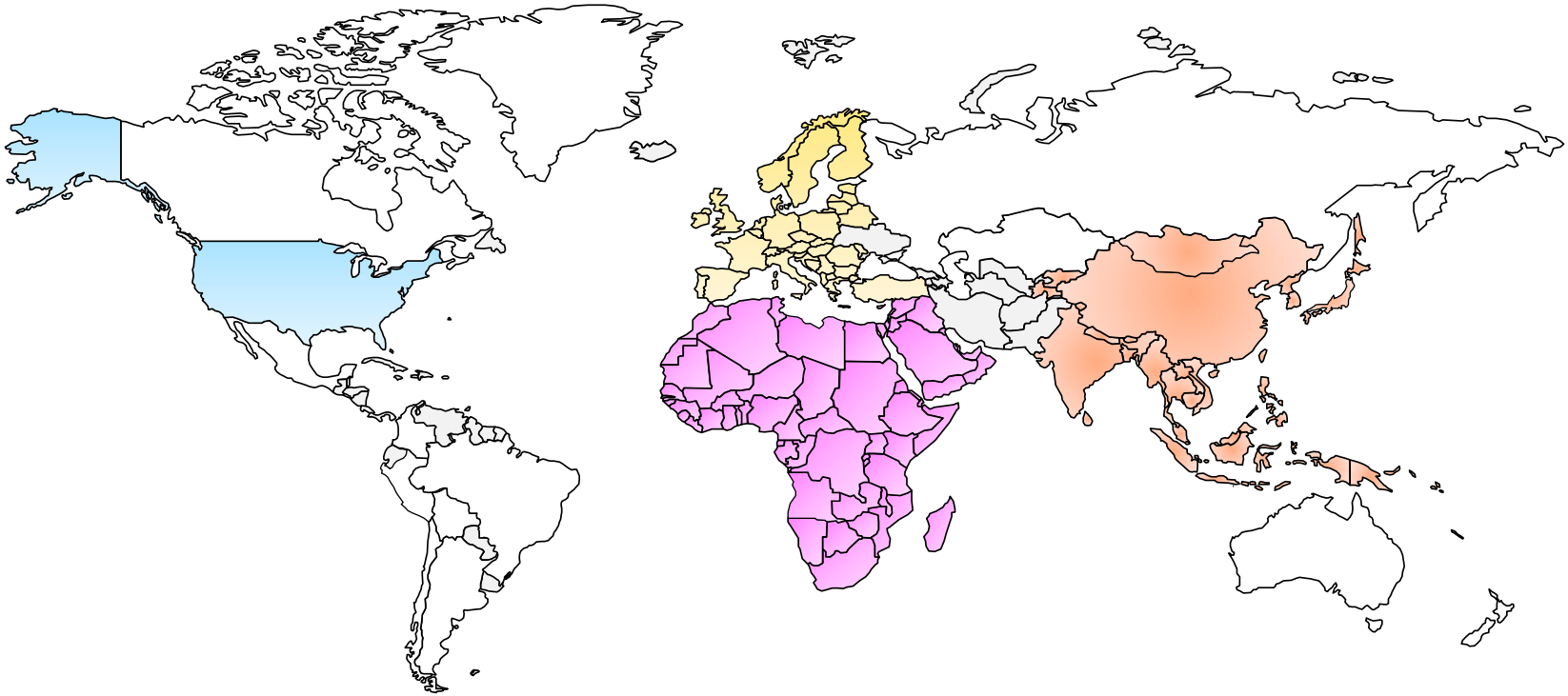
= control group consists of patients not part of the same clinical study



à For discussion and consideration throughout today's session!

Global Regulator Activities on RWD/RWE

Health Authority Focus on RWD Varies Across Regions



United States

Leveraging RWD for regulatory decisions is a key strategic priority for the FDA

- Legislative drivers direct FDA to establish framework and guidance
- RWD guidance already issued for regulatory decision making in different fields
- Long and significant experience with Sentinel System
- New RWE Committee for informal RWE discussions
- Release of code / technical roadmap for FDA's RWD mobile app
- Framework for RWE released in Dec 2018

"As the breadth and reliability of RWE increases, so do the opportunities for FDA to make use of this information……"
FDA Commissioner Scott Gottlieb, September 19, 2017

EMA RWD Initiatives (not exhaustive)

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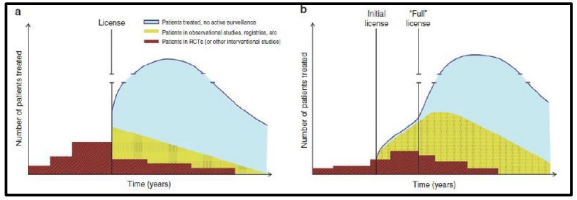
1. Adaptive Pathways

- Concept investigating prospectively planned adaptive approaches to licensing



The evolution of adaptiveness: balancing speed and evidence

nature REVIEWS DRUG DISCOVERY

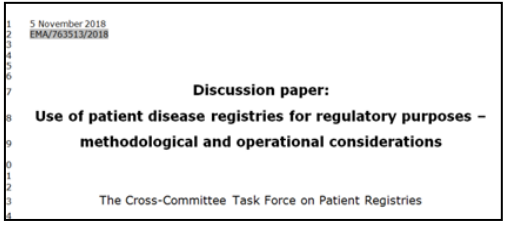
2. EMA/HMA Big Data Task Force

- Formed to describe big data landscape from a regulatory perspective

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

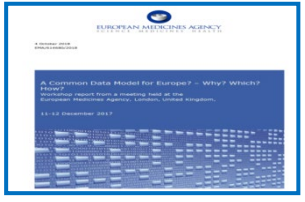
3. Patient Registry Initiative

- Aim to address challenges in using existing registries or establishing new ones



4. Building a RWD Ecosystem

- A common data model for Europe
- A Learning Healthcare system



Interest in RWD is Also Growing Throughout Asia

China
(NMPA/CCFDIE*)

Duke MARGOLIS CENTER for Health Policy

Japan
(PMDA)

India
(CDSCO)

Taiwan
(TFDA)

Duke MARGOLIS CENTER for Health Policy

Singapore
(HSA)

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**China Center for Food and Drug International Exchange, Affiliate to NMPA*

Global Regulator Perspectives on RWE

Perception of the “General” Position of Regulators

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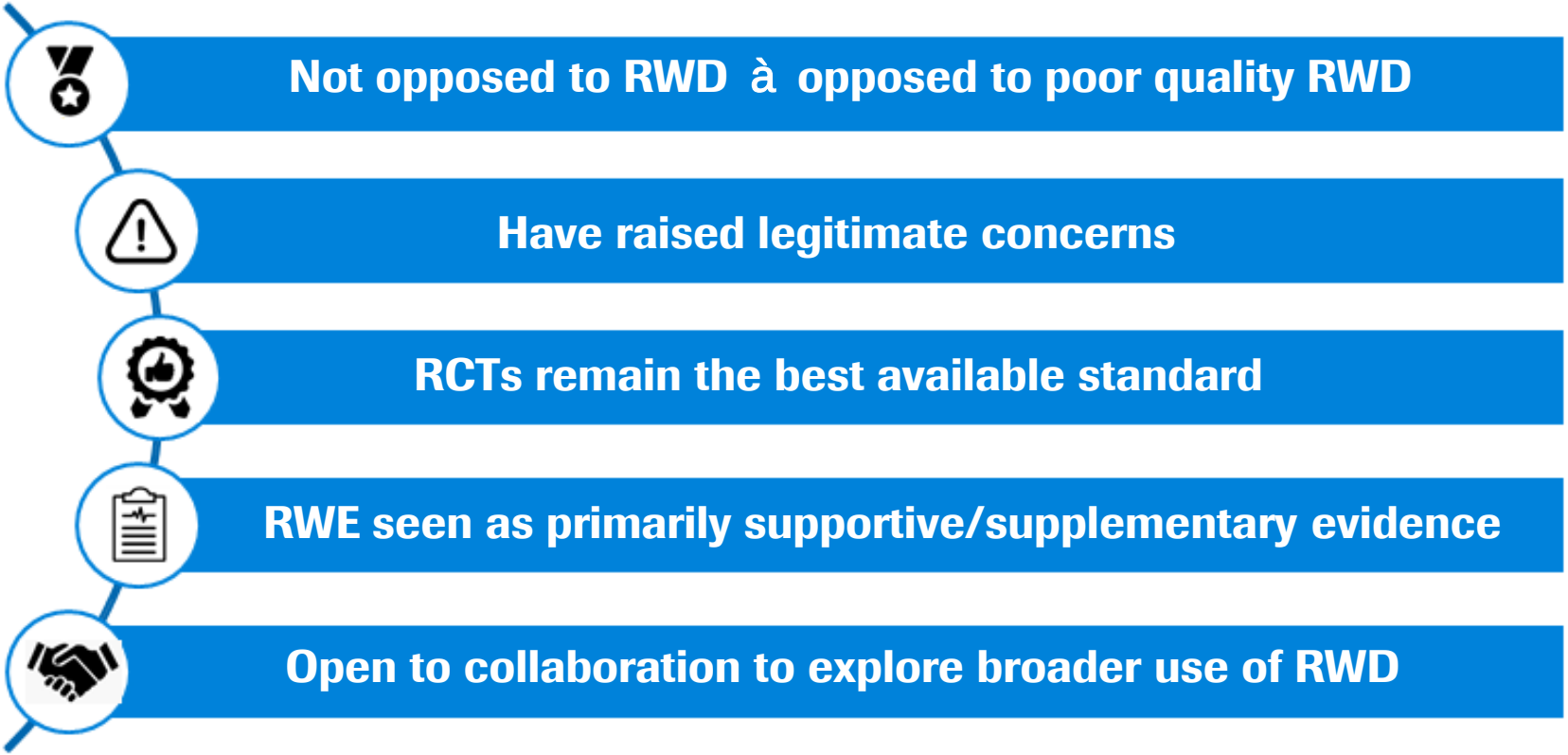

Where Have Regulators Accepted RWD?

The use of RWD to support regulatory decision making is **not new**

Decades worth of regulator experience with RWE:

- Ø **Post Approval**
- Ø **For safety signal evaluation / Pharmacovigilance**

"RWE is currently used extensively for evaluation of safety of marketed products, but there is very little historical use of RW experience in drug regulatory decisions about effectiveness"

Janet Woodcock, director of CDER

What about Efficacy and Effectiveness?

Roche

There is **lower acceptability** of RWD where the interest is **efficacy and effectiveness… but there are some examples…..**

FDA Approval History using RWE to Support Efficacy

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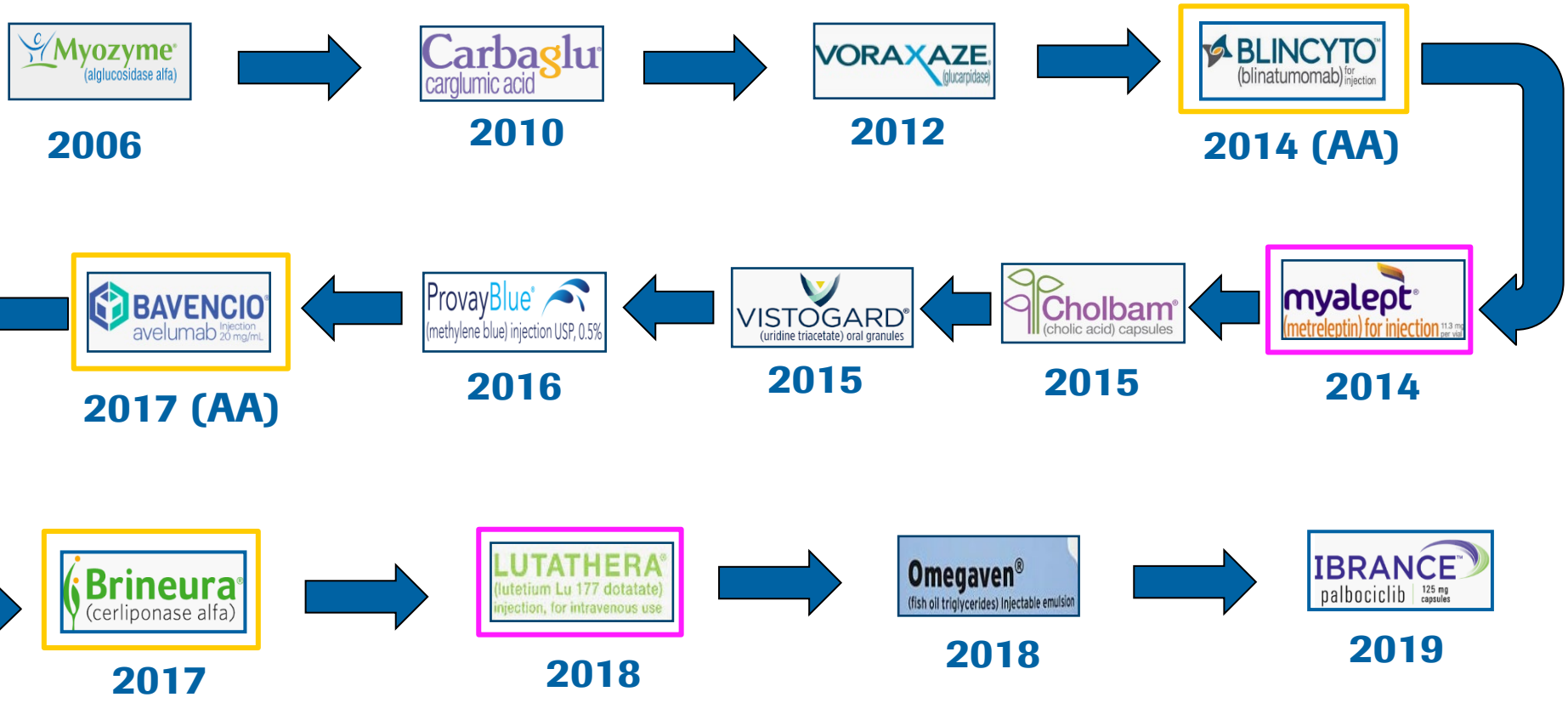


= RWE came from data collected under treatment IND or expanded access protocol

= Breakthrough Designation

These Approvals have things in Common…

- Cases involved single-arm trial + benchmark against aggregated external data
- Approvals limited to:
  - Ø **Rare/Orphan settings**
  - Ø **High unmet medical needs**
  - Ø **RCTs not feasible/ethical**
  - Ø **No satisfactory treatment**
  - Ø **Single arm effect substantial**

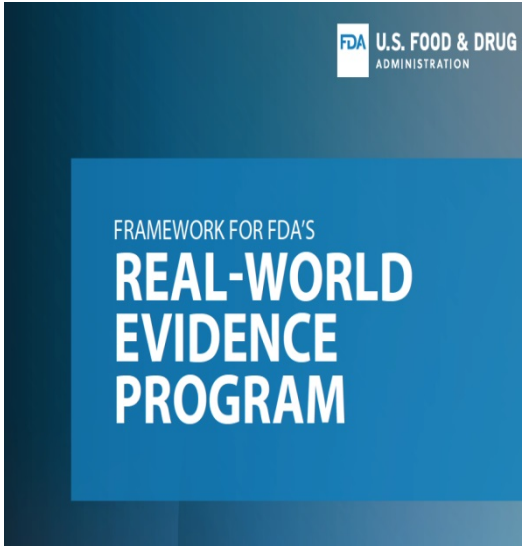
Rare space has provided an "early testing ground" for FDA's use of RWE in effectiveness decisions

"The FDA on a scale of 1 to 10 may be at a 9 or 10 for RWD use in rare diseases but may only at a 1 for RWE use in common diseases, especially if a traditional clinical trial could be done to show efficacy"

Rajeshwari Sridhara, director of the CDER Office of Biostatistics Division of Biometrics V

What does the FDA RWE Framework Say about External RWD Controls?

- Typically external control arms use data from **past traditional clinical trials but in some cases uses RWD**
- Limitations of external controls:
  - Selection of a comparable population
  - Lack of standardized diagnostic criteria or equivalent outcome measures
  - Variability in follow-up procedures
- Collection of RWD on patients **currently** receiving other treatments, **together with proper statistical methods**, **could improve the quality** of the external control data, provided the **relevant covariates are captured**
- FDA **may issue guidance** on the use of RWD for external controls



Ex-Regulator Recent Comments on External Controls

Tomas Salmonson (former chair of CHMP) DIA interview 2019

*"I would **prefer to see** a RCT with small numbers and not with same aim of P<0.05, than single arm trials vs. contemporary or historical controls…."*

*"…**but if we do single arm trials I think we can do better when it comes to creating the controls** – we need to have **the methodological discussions** around how to **generate robust data** to come to robust conclusions…."*

***"Randomisation of RWD within registry studies is perhaps a way forward**…"*

Stakeholder Requests for Initial Approval

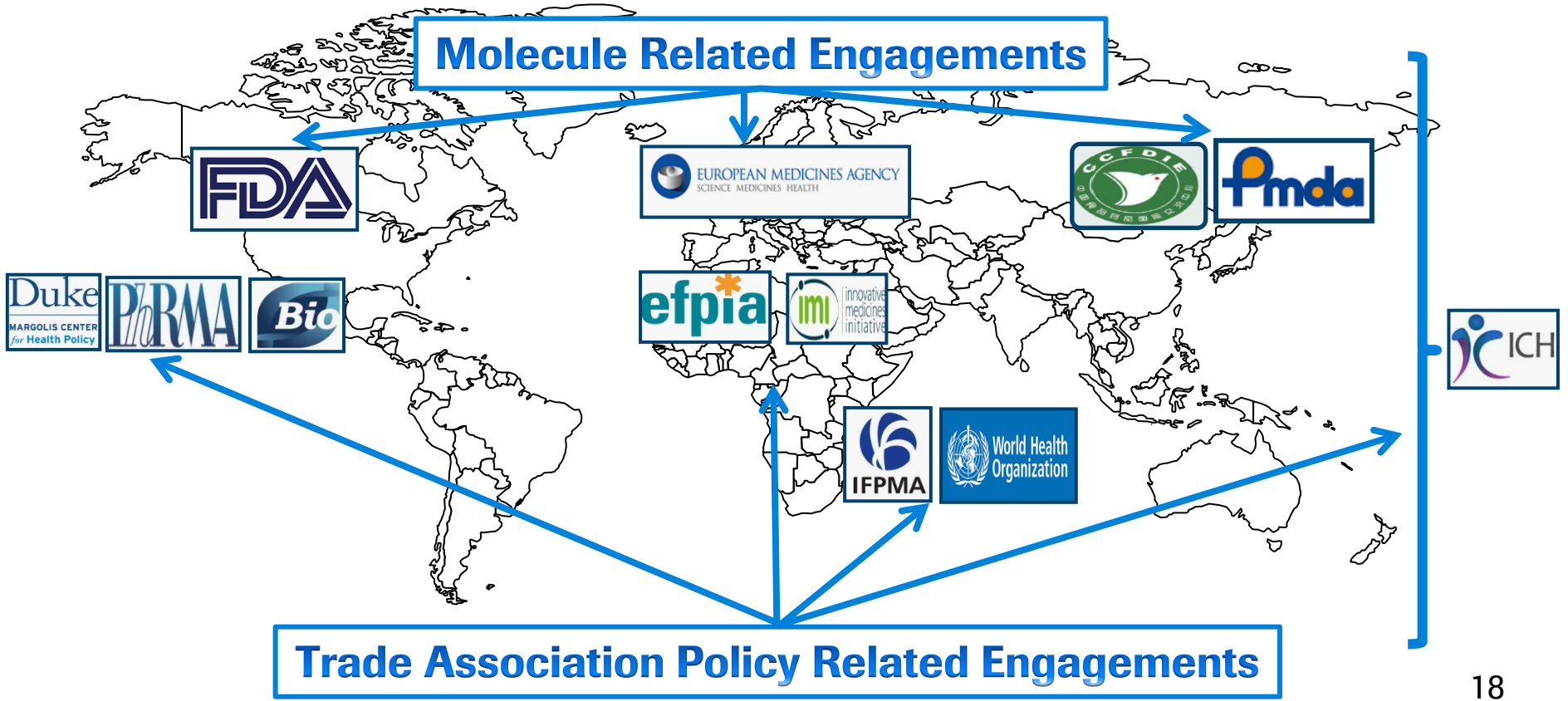
REGULATORS

- Linear thinking RWD study designs
- Endorse no one type of RWD over another
- Justifications for high quality RWD
- Early (and continued) multi-stakeholder dialogue
- Transparency of RWD studies
- Robust and consistent statistical methodologies

INDUSTRY

- Further transparency in HA decision making
- How is RWD quality assessed
- Frameworks / guidance on RWE
- Global harmonisation and convergence of guidance and standards where appropriate
- Options to discuss RWD proposals to advance the topic

Unprecedented Opportunities to Collaborate Across Industry and with Regulators/HTA bodies



Doing now what patients need next