

(NOVAS) ESTRATÉGIAS REGULAMENTARES

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Agradecimento: Professor Doutor Bruno Sepodes | Chair CHMP/EMA, FFUL

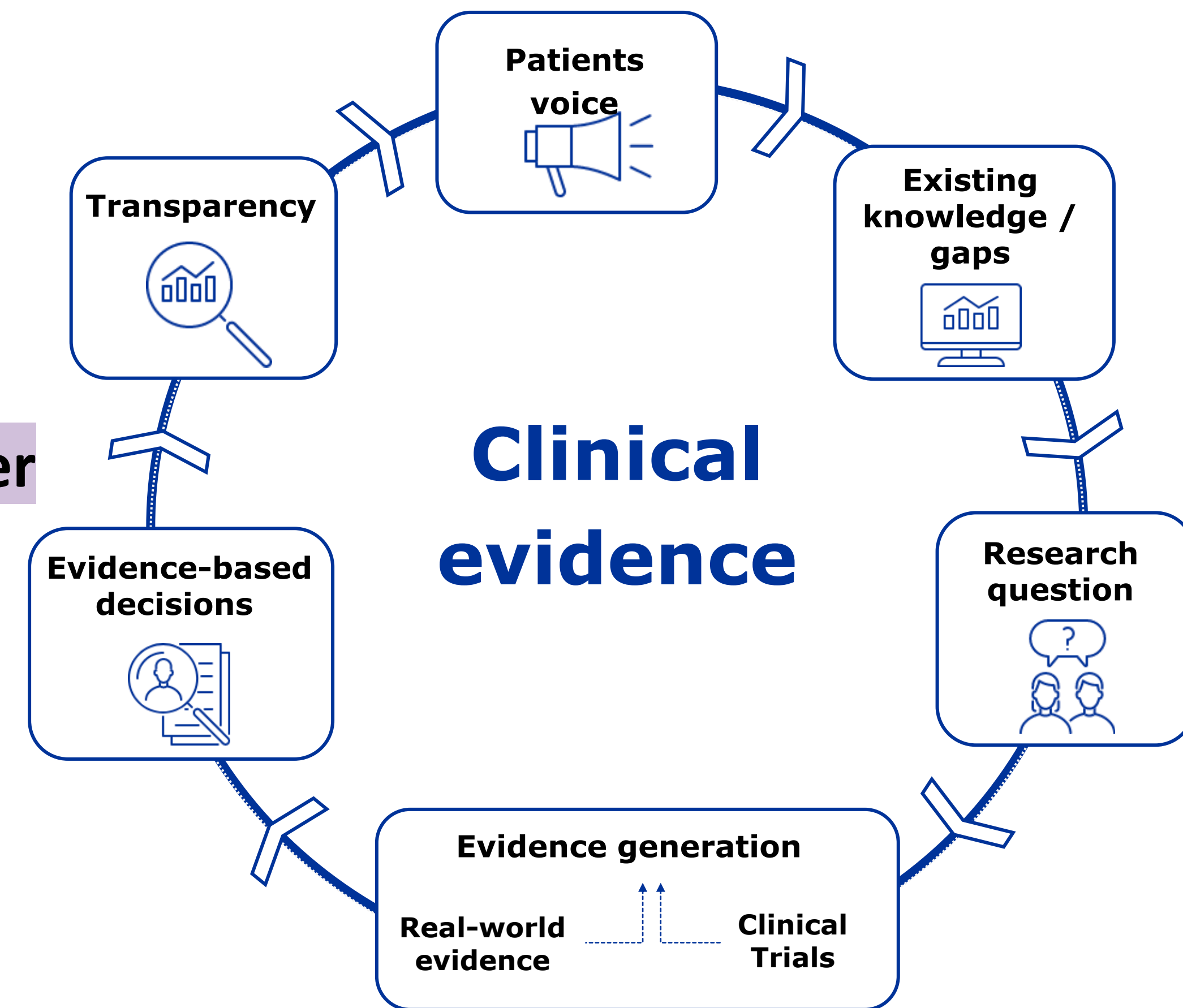


Disclaimers

- The views expressed in this presentation are my personal views and may not be understood or quoted as being made on behalf of or reflecting the position of the Portuguese Authority for Medicines and Health Products (INFARMED, I.P), the European Medicines Agency (EMA) or any of its committees or working parties/groups I am affiliated with.
- I declare having no conflict of interest.

The vision: clinical evidence 2030

- **Evidence generation** is planned and guided by data, knowledge and expertise
- **Research question drives evidence choice**: embraces spectrum of data and methods
- **Clinical trials remain core but are bigger, better and faster**
- **Real world evidence is enabled, and value is established**
- The **patient voice** guides every step of the way
- **Healthcare systems** are supported in their choices
- **High levels of transparency** underpin societal trust



Nature of R&D pipeline: *blockbuster* to *nichebuster*

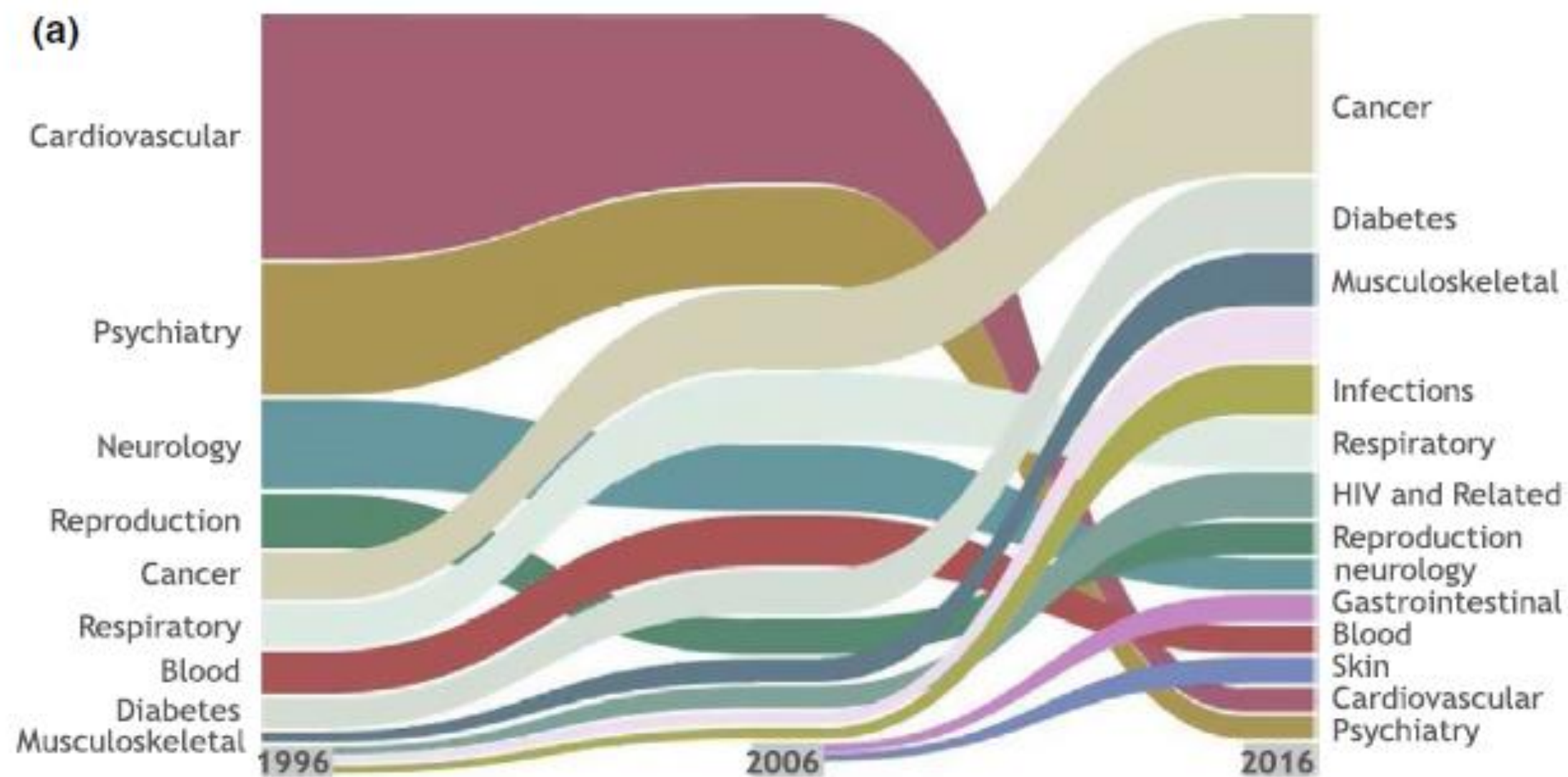
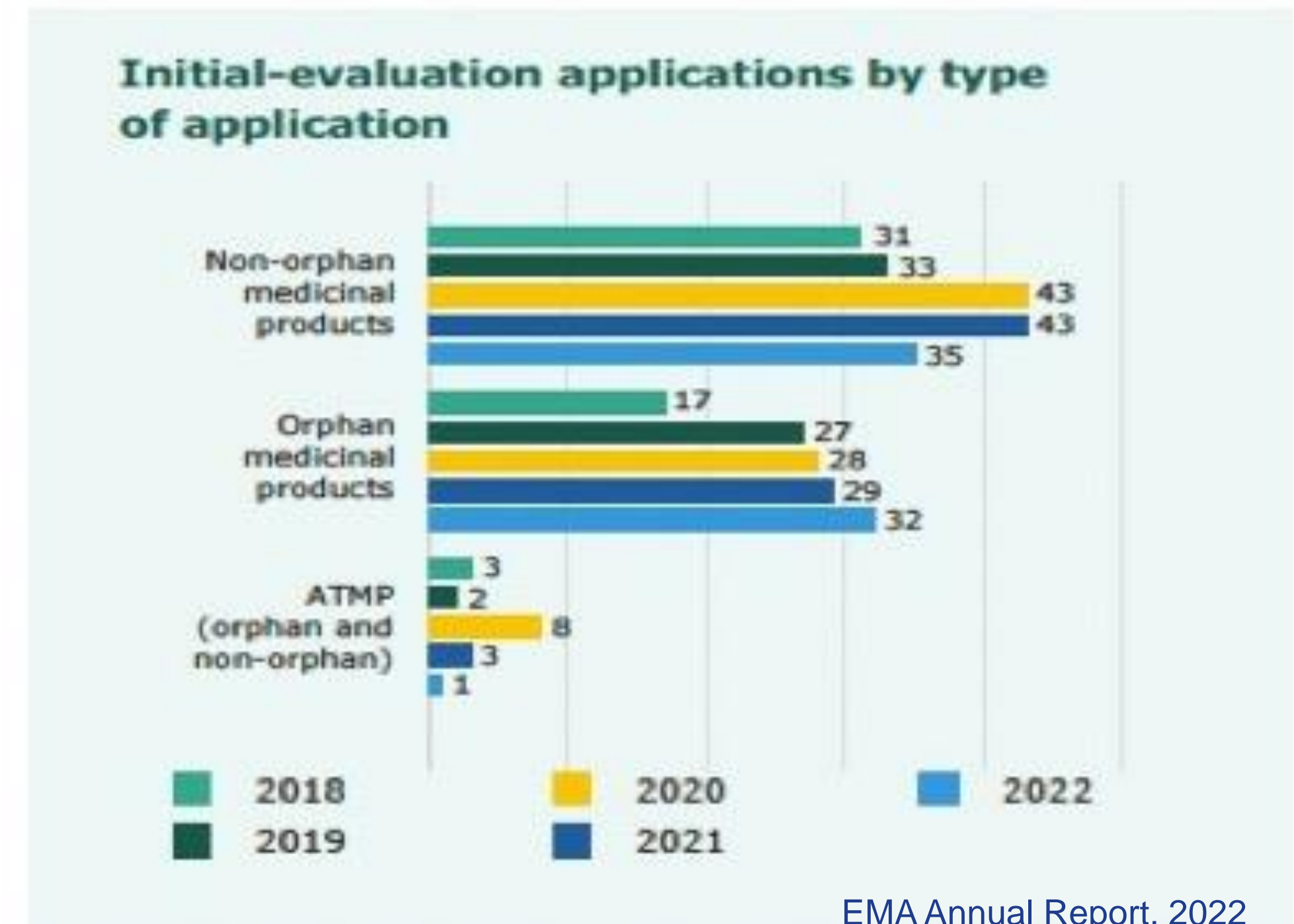


Figure 1 Therapeutic area trends. (a) United States share of revenue by therapeutic area, 1996–2



An increasing number of medicines orphan products/ATMPs for conditions with significant unmet need, face challenges when aligning with the traditional drug development pathway (e.g. traditional RCTs may be *unfeasible, unethical*, or less well suited to “precision medicines”).

Need to complement RCT data / addressing uncertainties in post-marketing phase with RWD (e.g. addressing safety concerns, providing supportive data and further contextualisation).

A single story of a continuum of tales in regulatory decision making

RCTs mainstay of drug efficacy and safety information for regulators/HTAs

Value of RWD is increasingly acknowledged

- Transform, accelerate and de-risk decision making
- Improve efficiency in design and conduct of trials
- Increase public health impact

Marketing Authorisation

- Contextualize study results
- Ensure generalisability of results to target population

Post-Authorisation

- Appreciate real-world value
- Long-term B/R balance

Data	Methodology	Trust/Transparency	Policy & Governance Environment
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Source: <https://copperbowl.de/Chess-Pieces-Tier-List-Cape-Fear-Games-61289.html>

Use case example

Comparative Analysis of Post-Authorization Measures for Advanced Medicinal Products Authorized in the European Union and in the United States of America Between 2009 and 2023

Diana Mandslay¹, Diogo Almeida^{1,2} , Adriana Marques^{1,2} , João Rocha^{1,2} , Frantisek Drafi^{3,4} , Bruno Sepodes^{1,2,†}  and Carla Torre^{1,2,*,†} 

In the current landscape, regulatory agencies face the challenge of ensuring the safety and efficacy of medicines addressing life-threatening conditions with technologies that are pronounced with advanced therapy medicinal products. Post-authorization measures for orphan drug designations are often applied, making post-authorization measures a source of uncertainties. We compared post-authorization measures imposed by the European Medicines Agency on ATMPs approvals, from requirements (PMRs) and EMA-imposed post-authorization measures documents was conducted. Descriptive analysis focused on study designs, and their status and registration rates. A total of 53 PMRs were imposed by the EMA, whereas the FDA imposed 27 PMRs. As of December 2023, 27 PMRs were indicated for FDA PMRs. Both agencies provided information on the study design for each PMR imposed.

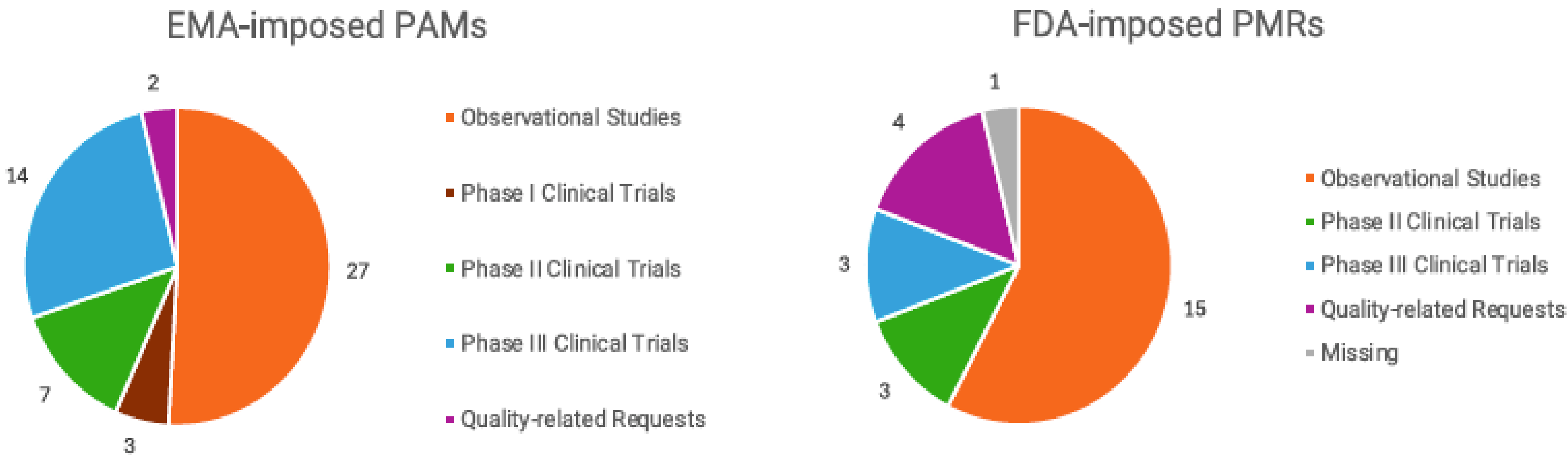
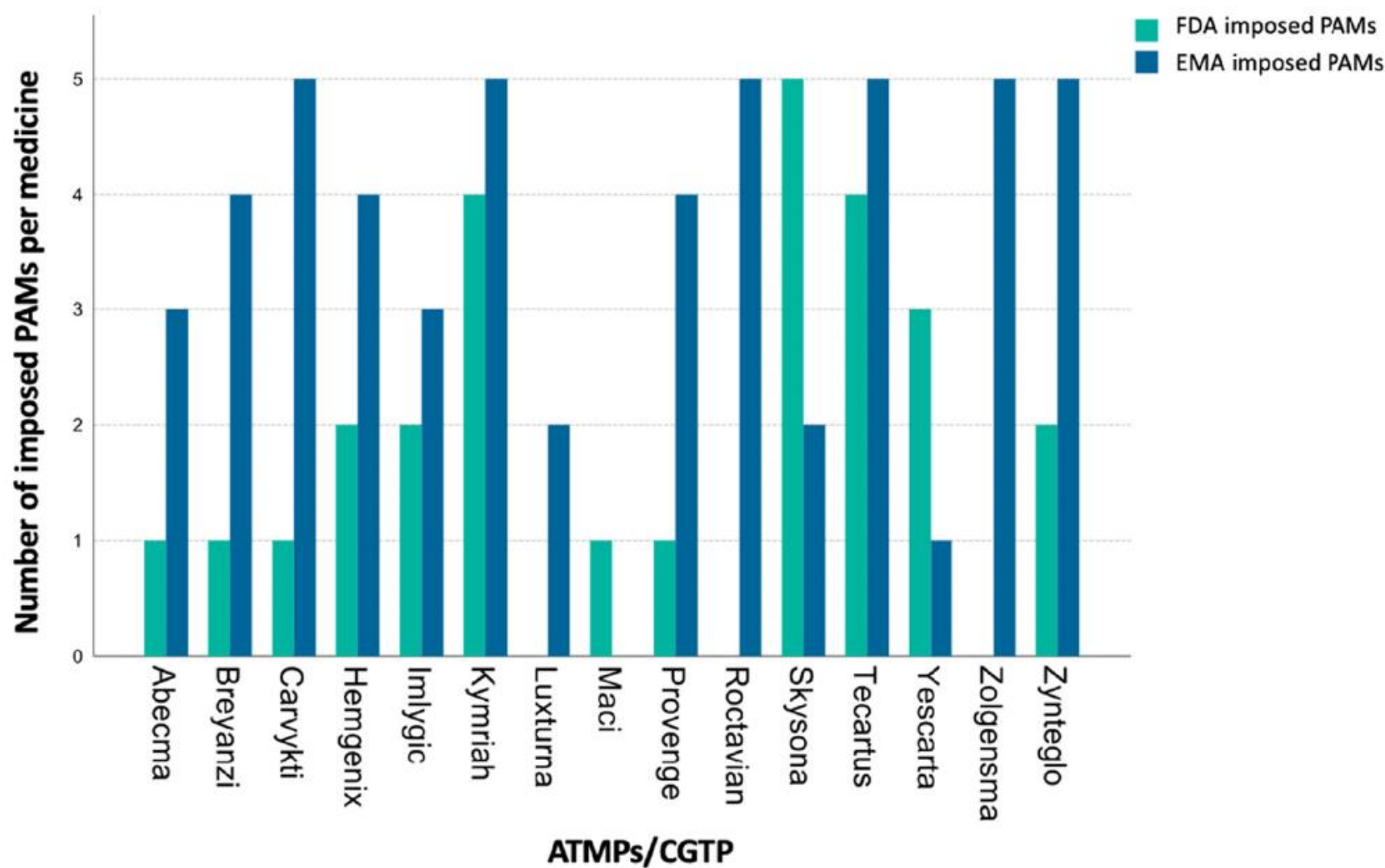


Figure 3 Study design for each PAM imposed by the EMA vs. the FDA. EMA, European Medicines Agency; FDA, Food and Drug Administration; PAM, Post-authorization Measure; PMR, Postmarket Requirement.

European Medicines Regulatory Network Strategy 2025

Check for updates

PERSPECTIVES

PERSPECTIVE

Real-World Evidence in EU Medicines Regulation: Enabling Use and Establishing Value

Peter Arlett^{1,*}, Jesper Kjaer², Karl Broich³ and Emer Cooke¹

We outline our vision that by 2025 the use of real-world evidence will have been enabled and the value will have been established across the spectrum of regulatory use cases. We are working to deliver this vision through collaboration where we leverage the best that different stakeholders can bring. This vision will support the development and use of better medicines for patients.

regulatory partners. This work also needs to be seen in the wider EU policy context, most notably the European Commission's plans for a European Health Data Space.⁷

Acknowledging different frameworks to conceptualise the challenges and opportunities of RWE, we believe the two main priorities for the European Union are to enable its use and establish its value for regulatory decision making. The EMRN is working to deliver on both priorities through a collaborative approach where we leverage the best that different stakeholders can bring, and where those stakeholders can complement the central role of industry in generating evidence.

ENABLING USE

To enable use, we are working on multiple fronts with our stakeholders, including patients, healthcare professionals, industry

DARWIN-EU® - Access to data from ~130 M patients in 2024

The diagram shows a map of Europe with lines connecting various countries to their respective data sources for DARWIN-EU. The countries and their data sources are:

- The Netherlands**: Integrated Primary Care Information, Netherlands Cancer Registry
- Belgium**: IQVIA Longitudinal Patient Database Belgium
- United Kingdom**: Clinical Practice Research Datalink (CPRD GOLD), UK BioBank
- France**: Bordeaux University Hospital, Système National des Données de Santé
- Portugal**: Unidade Local de Saúde de Matosinhos, Egas Moniz Health Alliance DataBase
- Spain**: SIDIAP, Parc Salut Mar Barcelona, Hospital del Mar (IMIM), BIFAP, Valencia Health System Integrated Database
- Norway**: Norwegian Linked Health Registries
- Finland**: FinOMOP
- Estonia**: University of Tartu (Biobank)
- Denmark**: Danish Health Data Registries (onboarding in progress)
- Germany**: IQVIA Disease Analyzer Germany
- Hungary**: Semmelweis University Clinical Data
- Croatia**: Croatian National Public Health Information System


STATE OF THE ART REVIEW

Real-World Evidence to Support EU Regulatory Decision Making—Results From a Pilot of Regulatory Use Cases

Stefanie Prilla^{1,*}, Sophie Groeneveld¹, Alexandra Pacurariu¹, María Clara Restrepo-Méndez¹, Patrice Verpillat¹, Carla Torre², Christian Gartner³, Peter G. M. Mol^{4,5}, Frauke Naumann-Winter⁶, Kieran C. Breen⁷, Nathalie Gault⁸, Liana Gross-Martirosyan⁵, Sylvie Benchetrit⁸, Brian Aylward⁹, Violeta Stoyanova-Beninska⁵, Maura O'Donovan⁹, Sabine Straus^{5,10}, Jesper Kjaer¹¹ and Peter Arlett¹

By 2025, the **use of RWE** will have been **enabled** and the **value** will have been **established** across the spectrum of regulatory use cases


Landscape of EU RWD/E guidance (list not exhaustive)



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

22 October 2021
EMA/426390/2021
Committee for Human Medicinal Products (CHMP)

Guideline on registry-based studies



ICH
harmonisation for better health

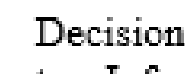
INTERNATIONAL COUNCIL FOR HARMONISATION OF TECHNICAL
REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED GUIDELINE

General Principles on Planning and Designing Pharmacoepidemiological Studies That
Utilize Real-World Data for Safety Assessment of a Medicine

M14

Draft version
Endorsed on day month year
Currently under public consultation



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Updated ICH Reflection Paper
April 2024

Pursuing Opportunities for Harmonization in Using Real-World Data to Generate Real-World Evidence, with a focus on Effectiveness of Medicines

Introduction

The role of real-world data (RWD) and real-world evidence (RWE) in supporting the evaluation of medicines across the different stages of their development and lifecycle is evolving [US Food and drug Administration (FDA), Framework for FDA's Real-World Evidence Program (2018) and FDA guidance Considerations for the Use of Real-World Data and Real-World Evidence to Support Regulatory Decision-Making for Drug and Biological Products (2023); Optimizing the Use of Real World Evidence to Inform Regulatory Decision-Making, Health Canada, Canada's 2019; Arlett et al., 2021; ENCePP Guide on Methodological Standards in Pharmacoepidemiology, latest version published].

In July 2022, the International Coalition of Medicines Regulatory Authorities expressed its strong support to strengthening international collaboration on activities to enable the use of RWE in regulatory decision-making [ICMRA, 2022]. This statement emphasises the engagement of regulatory agencies across the globe to address current gaps due to the lack of standardisation of RWD/RWE terminology and formats, the heterogeneity of RWD sources and data quality across RWD sources, and the various study designs used depending on the types of diseases, medicines (referred throughout as including drugs, vaccines, and other biologics), and regulatory contexts. Addressing these challenges should be supported by common definitions and best practices.

This Reflection Paper outlines a strategic approach for ICH to address some of these challenges. The goal is to further enable the integration of RWE into regulatory submissions and timely regulatory decision-making.

Patient voice in every step: for patients with patients

frontiers

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Leveraging patient experience
data to guide medicines
development, regulation, access
decisions and clinical care in the
EU

Diogo Almeida^{1,2}, Denise Umuhire³, Rosa Gonzalez-Quevedo⁴,
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Multi-stakeholder workshop: Patient experience data in medicines development and regulatory decision-making

21 September 2022, 10:00 – 16:30 (CEST), EMA, Amsterdam

Background and objectives

Patients have valuable insights and perspectives from living with a condition and its treatment. This includes symptoms, natural history, quality of life, unmet needs, which outcomes are important and preferences for future treatments. Input from patients, as users of medicines, can inform medicine development, enhance regulatory decision making and result in more patient-relevant outcomes.

EMA’s Regulatory Science Strategy to 2025 recognises the need to identify optimal approaches for engaging patients in medicines development and benefit-risk assessments, including the development of standards for designing, conducting, analysing and reporting relevant studies incorporating patient experience data for regulatory submission, and to elucidate how such data can best inform regulatory decisions.

This multistakeholder workshop will bring together patients, healthcare professionals, academia, regulators, and industry to discuss ways to improve the collection and use of patient experience data to achieve patient-centred medicine development and regulation.

frontiers

in Medicine

ORIGINAL RESEARCH

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The Added Value of Patient
Engagement in Early Dialogue at
EMA: Scientific Advice as a Case
Study

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frontiers

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A review of patient-reported
outcomes used for regulatory
approval of oncology medicinal
products in the European Union
between 2017 and 2020

Maria Manuel Teixeira^{1*}, Fábio Cardoso Borges²,
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Lisbon, Portugal

Regulators & HTA/payers: it's time to bridge and connect

Jansen E, et al. Value Health. 2022

Strengthening the Interface of Evidence-Based Decision Making Across European Regulators and Health Technology Assessment Bodies

Ella Jansen, MSc, Philip A. Hines, MSc, Michael Berntgen, PhD, Angela Brand, PhD

Table 3. Pairwise comparison of clinical evidence use between 8 EPARs and corresponding rapid REAs.

	EPAR (8)	Rapid REA (8)
Active comparator used	2	6
Active comparator and placebo used	0	0
Surrogate endpoint as primary endpoint in efficacy/effectiveness domain	4	1
QOL measurement present	6	5
Perceived importance of QOL measurement	2 secondary endpoint, 5 exploratory endpoint, 1 not mentioned	6 critical endpoint, 1 secondary endpoint, 1 not mentioned
Subgroup analysis present	8	7
Discussion on reasons to include certain subgroup analyses	2 and 4 only partially	5
Assessment of risk of bias/strength of evidence reported	2	8
Requests for additional information fulfilled by the developer	7 and 1 not applicable	3

EPAR indicates European Public Assessment Report; QOL, quality of life; REA, relative effectiveness assessment.

- Pre-approval joint advice procedures are successful and highly valued by all stakeholders
- Information exchange at the time of regulatory decision is coming together: the EPAR can be further optimised
- Potential to further improve the evidence utilization across stakeholders to **avoid duplication and streamline decision making**, to **ultimately improve access to medicines** for European patients.



- DARWIN-EU may provide interesting opportunities for payers to receive RWD/RWE on medicines that may be used as part of their decision-making
 - Collaboration on post-licensing - pilots in oncology (2023/4)

Regulatory/HTA interface under the HTA regulation



Joint clinical assessment of medicinal products: Submission of early information by health technology developers

After 12 January 2025, medicinal products falling under the scope of Article 7(2), point (a) of [Regulation \(EU\) 2021/2282](#) (the HTA Regulation) will be subject to a Joint Clinical Assessment (JCA). Initially, the JCA will concern medicinal products with new active substances for which the therapeutic indication is the treatment of cancer as well as advanced therapy medicinal products. As of 13 January 2028, all medicinal products designated as orphan medicinal products and, as of 13 January 2030, all other medicinal products falling under the scope of Article 7 of Regulation 2021/2282 are also subject to JCA.

The EMA published [guidance](#) on 21 June 2024 to applicants/health technology developers on how to declare in the EMA Letter of Intent (via the [Pre-submission request form](#)) whether their application falls under the scope of the Health Technology Assessment Regulation ((EU) 2021/2282 Article 7) and, therefore, is subject to JCA. The Member State Coordination Group on Health Technology Assessment published a document entitled "[Scientific specifications of medicinal products subject to joint clinical assessments](#)" to support identification of products subject to JCA from 2025.

Requirements in the Implementing Act on Joint Clinical Assessment (medicinal products)

Exchange of information with EMA (acc to Article 3)

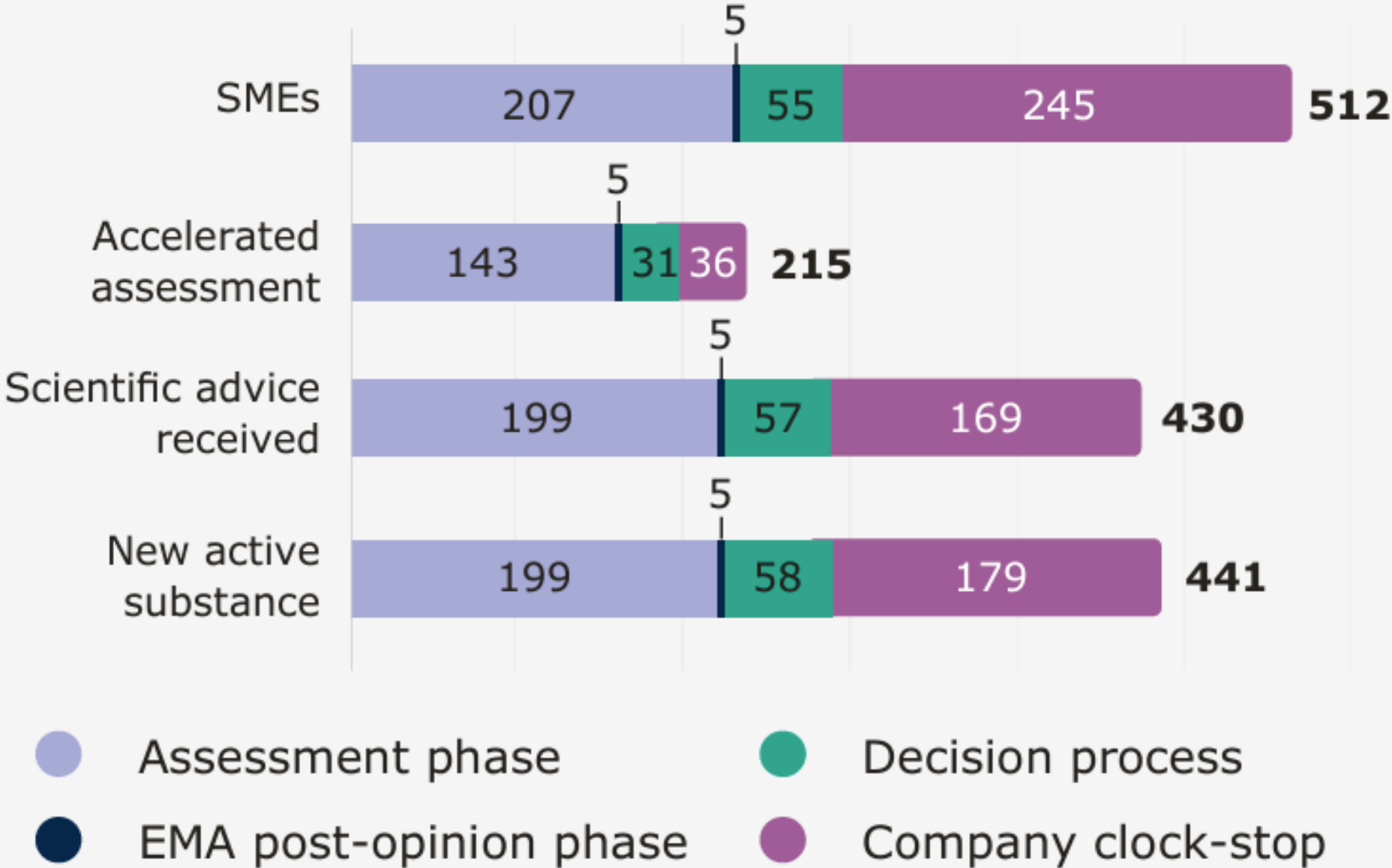
- Notification of HTA secretariat about MAA / EoI submission in scope of JCA
- Information about positive validation and timelines
- During the assessment, information about changes to timelines and substantial questions / outstanding issues impacting the therapeutic indication
- Provision of CHMP Opinion (AR and SmPC)

As of 13 January 2025, all medicinal products falling under the scope of Article 7 of [Regulation \(EU\) 2021/2282](#), for which the applicant declares in its application for marketing authorisation that it contains a new active substance and the therapeutic indication is the treatment of cancer and those that concern ATMPs are subject to JCA.

MAA – Marketing Authorisation Application; EoI = Extension of Indications;
AR = Assessment Report; SmPC = Summary of Products Characteristics

Improving efficiency of approval process for new medicines in the EU

Average number of days for centralised procedure - subset (2023)



- Only **35% of MAAs submitted on time** (i.e. as per the date indicated on the letter of intent from the applicant).
- 2018-2022: 30-40%
- **42% of companies requested more time** to respond to questions from EMA's scientific committees during the assessment ('**extended clock-stop**') because their data was not mature enough when it was submitted to EMA.
- **Average duration of clock-stops for initial MAAs: 198 days** (comparable to the average time of assessment (204 days).
- 2022: the average clock-stop was longer (205 days) than the assessment time (196 days).

Ongoing measures that aim to ensure the sustainability of the EU regulatory network

Reinforcing best practices for requests for clock-stop extensions, streamlined templates, better guidance for assessors, closer dialogue with applicants (...)

Regulatory science research is key to system improvement & innovation

EDITORIAL



Regulatory science: Regulation is too important to leave it to the regulators

On 19 December 2018, the European Medicines Agency (EMA) published its draft "Regulatory Science to 2025" strategy for a 6-month public consultation. In this EMA publication, regulatory science has been defined as "the range of scientific disciplines that are applied to the quality, safety and efficacy assessment of medicinal products and

of being too risk averse in the interest of giving patients access to new promising therapeutic options.³

Reality of regulatory decision making shows that this is not always a straightforward yes or no. Scanning the EMA website for European public assessment reports (EPARs) makes this very visible in situations

Trust in the robustness of data, trust in behavior of stakeholders (i.e., drug developers, investigators, and regulators), or trust in the rigor of regulatory decision making have always been critical to regulatory sciences, also from the perspective of how to ensure trust and how to tandem trust with control.

Investment in regulatory science is needed to bridge and to cement

REVIEW

The Evolution of Drug Regulatory Sciences in the Netherlands: More than a Country Report

Anna M. G. Pasmooij^{1,2,3,*} , Peter G. M. Mol^{1,3,4} , Jacob Cornelis Bot^{3,5,6}  and Hubert G. M. Leufkens^{2,3,6} 

In the Netherlands, a review, we present and that led to medicines research (i) TI Pharma E Science Network dynamic evolution pharmacovigilance sciences quest science, contribution of a new medicine national agency

Table 1 Listing of relevant regulatory sciences research topics

Domain	Research topics
Quality/CMC	Quality attributes for biosimilars, child/elderly friendly formulations, drug shortages, quality by design, bedside manufacturing/ATMPs
Non-clinical	Preclinical data as predictor for clinical outcomes, 3Rs in animal studies, PK/PD modelling, informative animal free toxicology models such as better toxicology models/organ on a chip and organoids, special populations (ICH S11), diagnostics and screening, data science
Clinical	Clinical evidence generation (small populations, high medical need), trial design (basket, platform), non-inferiority studies, biomarkers, endpoints
Post-approval	Risk management plans, safety communication, risk minimisation, alignment with HTA, pharmacovigilance strategies, registries/RWD
System	Benefit–risk, decision making, scientific advice, expedited/adaptive pathways, access to medicines, ethics/human rights, patient preference

Investment in regulatory science is needed to bridge and to cement

REVIEW

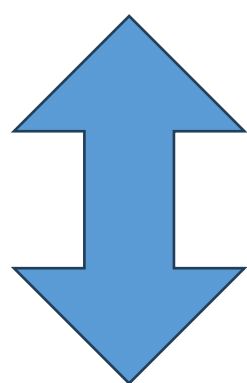
The Evolution of Drug Regulatory Sciences in the Netherlands: More than a Country Report

Anna M. G. Pasmooij^{1,2,3,*} , Peter G. M. Mol^{1,3,4} , Jacob Cornelis Bot^{3,5,6}  and Hubert G. M. Leufkens^{2,3,6} 

In the Netherlands, drug regulatory science is a vibrant national and internationally oriented community. In this

This paper is more than a country report. It is a lens through which regulatory sciences across scientific disciplines, stakeholders, and various societal needs have evolutionised in a single country. Inspiration came from many other jurisdictions, also from outside Europe, for example, the United States and Japan. The European map for regulatory sciences is getting richer and richer with, beyond the Netherlands, strong hubs in Copenhagen, Lisbon, Leuven and elsewhere.^{65,66,84–86} Also regulatory au-

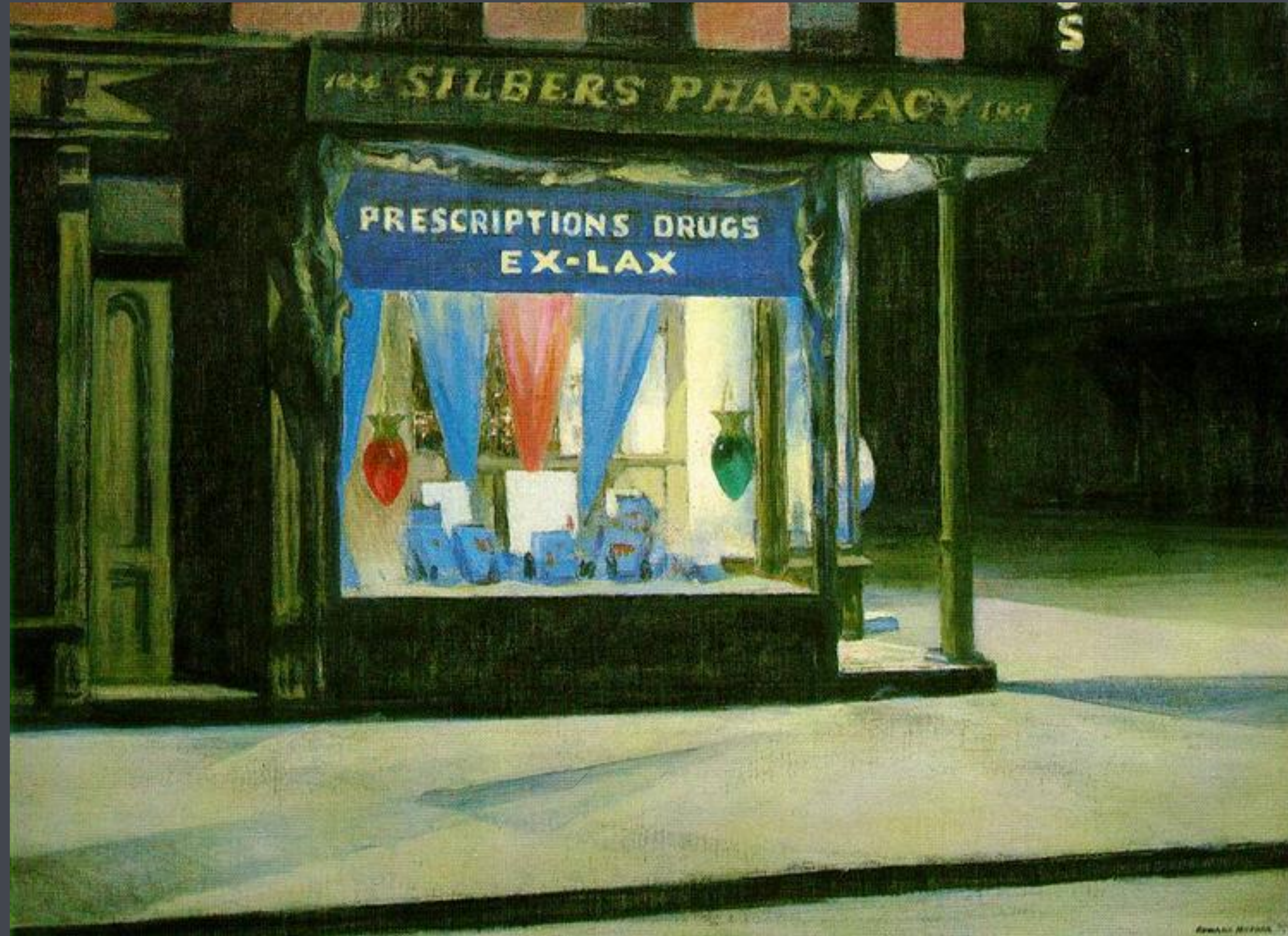
ACADEMIA



Enabling and leveraging research and innovation in regulatory science



Regulatory science makes medicines work



Drug Store, Edward Hopper (1927)