Perspectives on Rare Disease Landscape – Outputs from CIRS work

Magda Bujar, PhD, Senior Manager, Regulatory Programme & Strategic Partnerships,
Juan Lara, Senior Research Analyst
Anna Somuyiwa, Head

November 2023

Agenda

01 Introduction to CIRS and work in rare diseases

02 CIRS data – trend analysis on rare diseases including use of facilitated regulatory pathways and divergent decisions

03 CIRS October Workshop on rare diseases - recommendations

04 Data availability within CIRS and opportunities

About CIRS

Mission

To maintain a leadership role in identifying and applying scientific principles for the purpose of advancing regulatory and health technology assessment (HTA) policies and processes in developing and facilitating access to pharmaceutical products

35+ yrs experience in bringing **global** industry, regulators, HTA bodies, payers, academics and others together in a **neutral** atmosphere to identify and address key issues in the development, licensing and reimbursement of medicines.

Subsidiary of Clarivate plc – **operate independently** as a non-profit. Financed by industry membership fees, special projects, grants e.g., from regulators, HTA bodies, Bill and Melinda Gates Foundation

See CIRS Agenda: https://cirsci.org/download/agenda-2023/

CIRS member companies

20+ Global R&D Companies		
USA	**Europe**	**Japan**
AbbVie	AstraZeneca	Astellas
Amgen	Bayer	Eisai
Biogen	Boehringer Ingelheim	Takeda
Biomarin	GlaxoSmithKline	
BridgeBio	Ipsen	
Eli Lilly and Co.	Leo	
Johnson & Johnson	Novartis	
Merck & Co	Novo Nordisk	
Pfizer	Roche	
Pacira	Sanofi	
Regeneron		
Ultragenyx		

Participants: Regulatory agencies

Africa

Country	Authority
Egypt	EDA
Ethiopia	EFDA
Ghana	FDAG
Kenya	PPB
Mali	DPM
Liberia	LMHRA
Nigeria	NAFDAC
Rwanda	RFDA
Senegal	MoHP
South Africa	SAHPRA
Tanzania	TMMDA
Zambia	ZAMRA
Zimbabwe	MCAZ
Regional Initiatives *(and at member state level)*	Zazibona/SADC EAC ECOWAS

Americas

Country	Authority
Argentina	ANMAT
Brazil	ANVISA
Canada	Health Canada
Chile	ANAMED
Colombia	INVIMA
Cuba	CECMED
Dominican Republic	DIGEMAPS
Ecuador	ARCSA
El Salvador	DNM
Haiti	DPM/MT-MSPP
Mexico	COFEPRIS
Peru	DIGEMID
USA	FDA
Regional Initiatives	CARICOM-CRS PAHO SICA

EMEA

Country	Authority
Denmark	DKMA
EU	EMA
Ireland	HPRA
Israel	MoH
Jordan	JFDA
Saudi Arabia	SFDA
Sweden	MPA
Switzerland	Swissmedic
The Netherlands	MEB
Turkey	TITCK
United Arab Emirates	MOHAP
United Kingdom	MHRA
Regional Initiatives	GHC

Asia

Country	Authority
Australia	TGA
China	NMPA; CDE
Chinese Taipei	TFDA; CDE
India	CDSCO
Indonesia	NAFDC
Japan	MHLW, PMDA
Malaysia	NPRA
Philippines	PFDA
Singapore	HAS
Thailand	TFDA
Vietnam	DAV
Regional Initiatives	APEC ASEAN

CIRS Scientific Advisory Council (SAC)

Chair: Adjunct Prof John Skerritt, University of Sydney, Australia
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Dr Charlie Preston, Senior Programme Officer, Regulatory Affairs, Bill and Melinda Gates Foundation
Karen Reynolds Director General, Pharmaceutical Drugs Directorate, Health Canada
Mr Naoyuki Yasuda, Associate Executive Director for International Programs (PMDA), Japan
Dr Xie Songmei, Deputy Director of Clinical Department Center for Drug Evaluation, National Medical Products Administration (NMPA), China
Dr Steffen Thirstrup, Chief Medical Officer, European Medicines Agency (EMA)
Dr Fabio Bisordi, Global Head International Regulatory Policy, Roche
Jeffrey Francer, Vice President, Head of Global Regulatory Policy and Strategy, Global Regulatory Affairs, Eli Lilly and Co, US
Adrian Griffin, Vice President for HTA Policy Johnson & Johnson
Dr David Jefferys, SVP, Head of Global Regulatory, Eisai Europe
Jerry Stewart, Chief Medical Officer and Senior Vice President, Global Medical, Regulatory & Quality, GlaxoSmithKline
Dr Jacques Mascaro, Senior Vice President, Oncology Regulatory Science, Strategy and Excellence, AstraZeneca
Judith MacDonald, Head of International Regulatory Policy, Global Regulatory Policy and Intelligence, Pfizer
Natalie Tolli, Vice President, Regulatory Affairs (Regulatory International, Regulatory Policy & Intelligence), Abbvie
Dr Max Wegner, Senior Vice President, Head of Regulatory Affairs, Bayer
Prof Stuart Walker, Founder and Special Advisor, CIRS

Specialist Advisors:
Dr Thomas Lonngren, Former Executive Director, EMA
Dr Murray Lumpkin, Deputy Director, Integrated Development, and Lead for Global Regulatory Systems Initiatives, Bill and Melinda Gates Foundation
Prof Mamoru Narukawa, Professor, Pharmaceutical Medicine, Kitasato University Graduate School of Pharmaceutical Sciences, Japan
Dr Tomas Salmonson, Former Chair, CHMP/EMA
Dr Joseph Scheeren, Former President and CEO, Critical Path Institute

Meet the CIRS team

Anna Somuyiwa
Head

Dr Neil McAuslane
Director

Dr Magda Bujar
Senior Manager, Regulatory Programme and Strategic Partnerships

Dr Tina Wang
Senior Manager, HTA Programme and Strategic Partnerships

Gill Hepton
Administrator

Prof Stuart Walker
Founder and Senior Advisor*

Dr Jenny Sharpe
Senior Scientific Writer

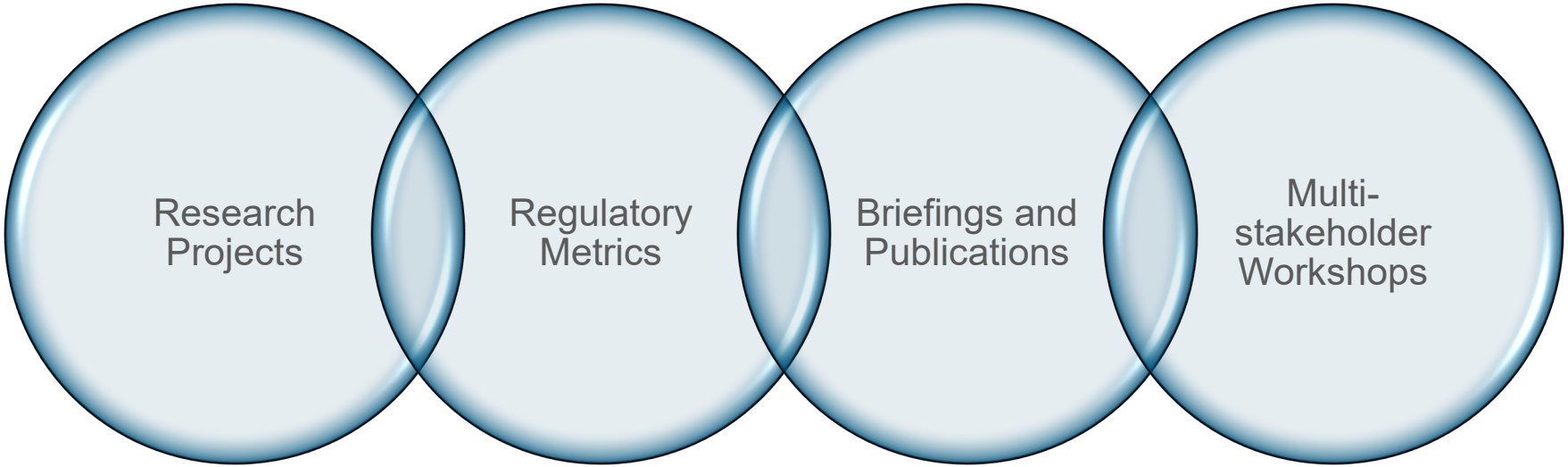
Adem Kermad
Senior Research Analyst

Juan Lara
Senior Research Analyst

Dr Belén Sola Barrado
Research Analyst

Dr Mario Alanis
Senior Consultant*

CIRS work in rare disease



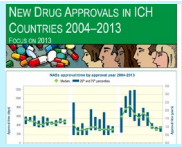
Timeline of CIRS metrics activities – focus on regulatory benchmarking

First full-scale benchmarking study with FDA, EMA, Health Canada, Swissmedic and TGA.

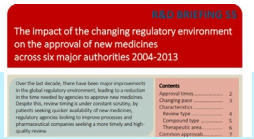
Identified **key milestones in the review process**.

Presentation of agency benchmarking results highlighted **importance of quality of review, in addition to time**.

Benchmarking study won award for most downloaded publication in *TIRS* journal.



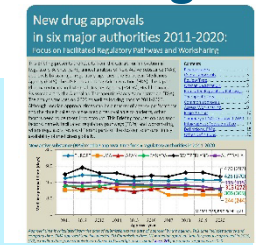
Annual benchmarking of FDA, EMA and PMDA using information from the public domain.



Facilitated Regulatory Pathways included in annual benchmarking

Swissmedic, Health Canada and TGA added to annual benchmarking.

Worksharing analysis of Access and Orbis included in benchmarking



Real world data and patient engagement included as part of benchmarking

2000 2004 2008 2012 2016 2020

1998 2002 2006 2010 2014 2018 2022

Preliminary discussions with industry to initiate **Emerging markets (EM) Programme.**

EM Industry Benchmarking Programme initiated (continued at present).

Approached by EM countries to initiate an **agency benchmarking programme**.

Optimising Efficiencies in Regulatory Agencies (OpERA) programme initiated

BMGF funding awarded to expand OpERA regulatory strengthening.

OpERA work expanded to 20+ countries and regional assessment initiatives in Asia, Latin America, Africa and the Middle East

CIRS tools connected to several of the sub-indicators within the WHO GBT

OpERA expanded to 35+ countries with a focus on regional work

Emerging market programme renamed Growth and Emerging Markets Programme and added new focus areas e.g. reliance

Maturing agency benchmarking – data directly from companies or agencies

CIRS 6 Agency Briefing

- CIRS has been benchmarking regulatory agencies since 2002 using a methodology developed with agencies (Hirako et al., 2007) to ensure like-for-like comparisons.
- The resulting analyses, published annually since 2012, give unique insights into regulatory processes and practices, identify where improvements can be made and inform company and agency strategies.
- Data is collected from the public domain on New Active Substances for:

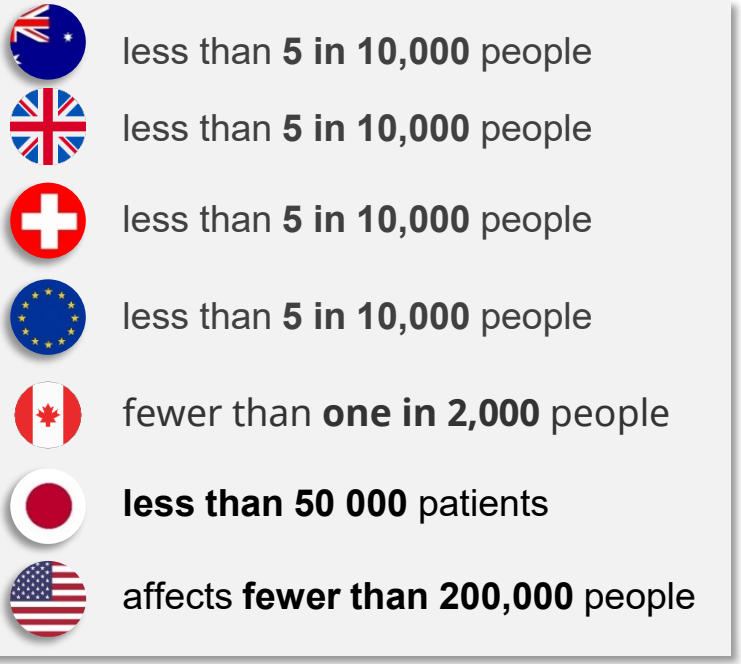
EMA  FDA  PMDA  Canada  Swiss  Aus TGA 

- Collection/validation for Brazil + China data from public domain is underway

Orphan drug designations

Drugs for **Rare Diseases** are medicinal products intended for the *diagnosis, prevention, o* *treatment* of **rare diseases or disease subtypes.**

- **Orphan drug** designation is used by regulatory agencies to facilitate approval of rare disease drugs
- For the purpose of this presentation – we will focus on orphan drugs
- **NOTE:** CIRS does not currently tag specifically which drug is intended to treat a rare disease, but it may be possible to assess this by evaluating the indication which is currently collected by CIRS



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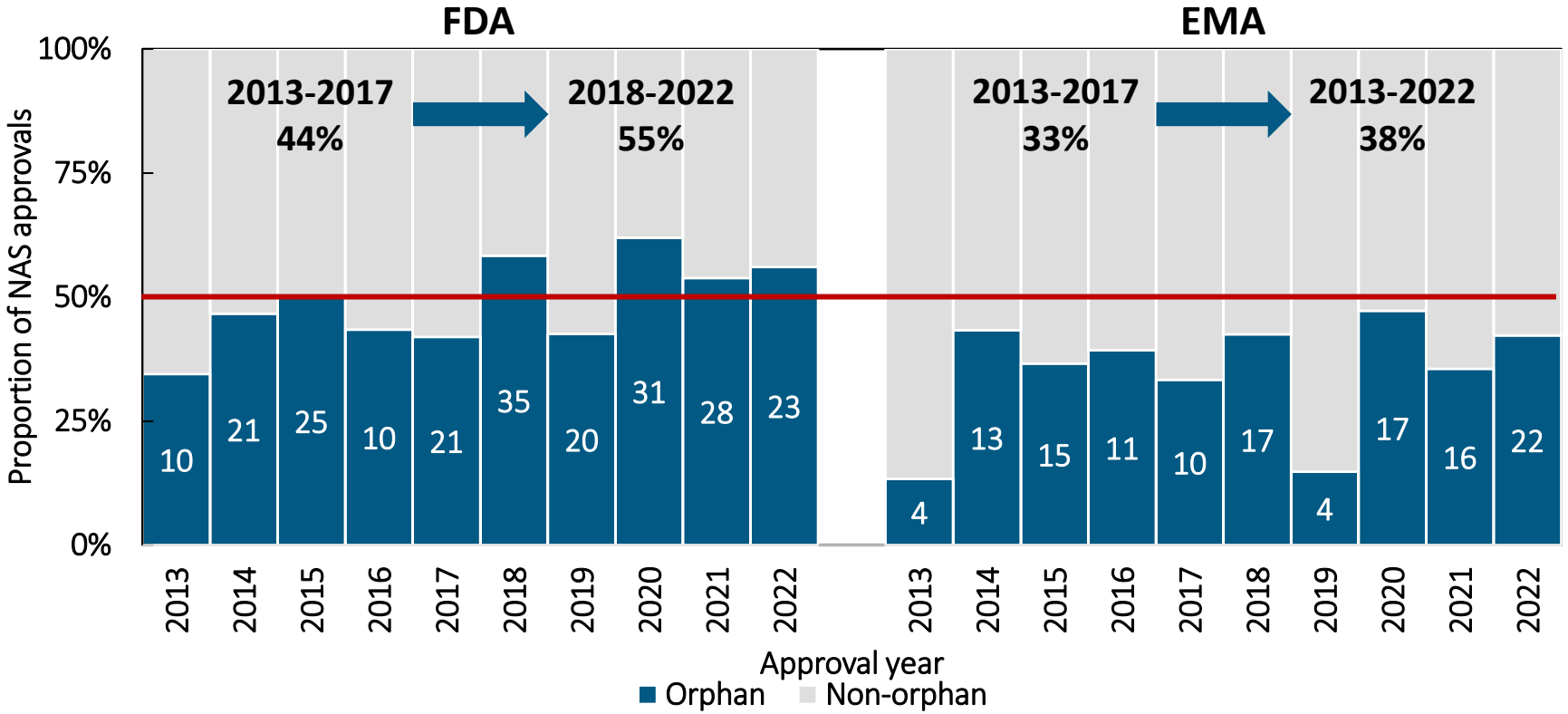
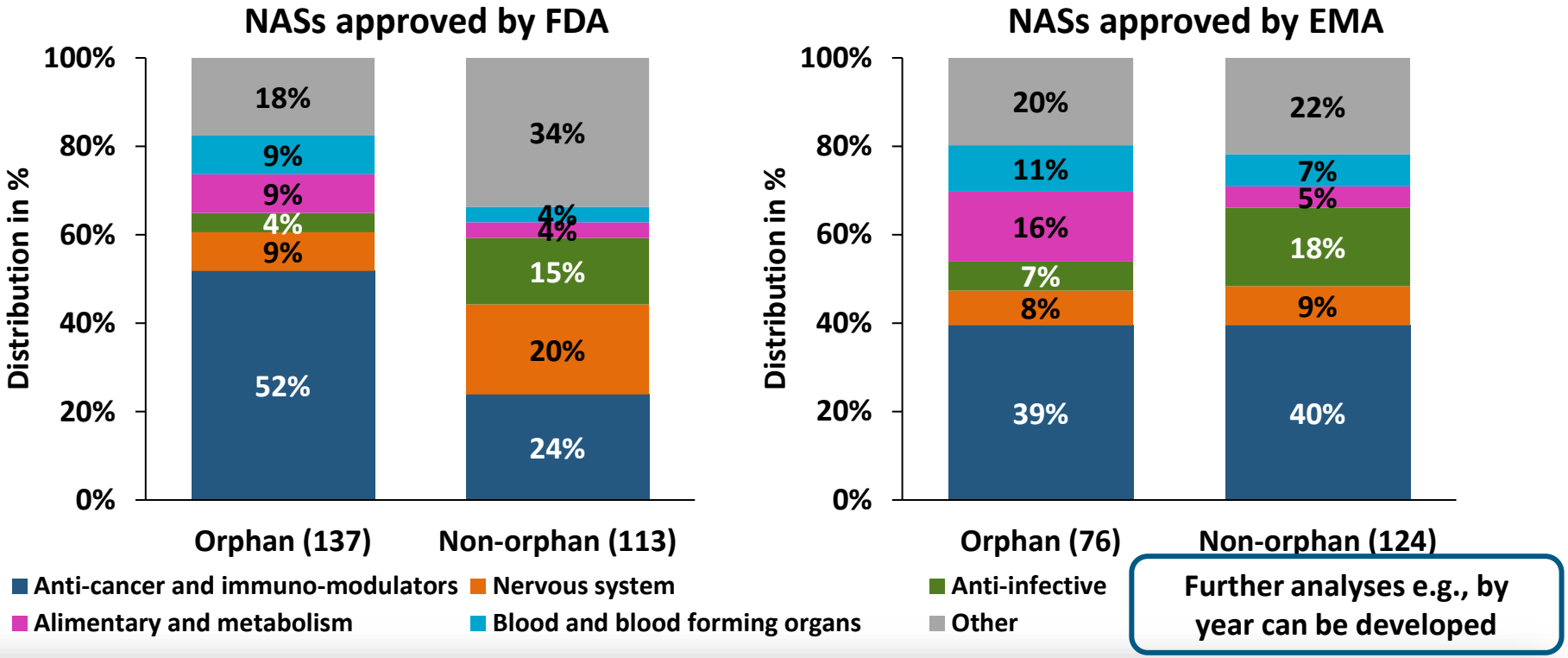
Proportion of orphan and non-orphan New Active Substance (NAS) approved by FDA and EMA in the last decade.

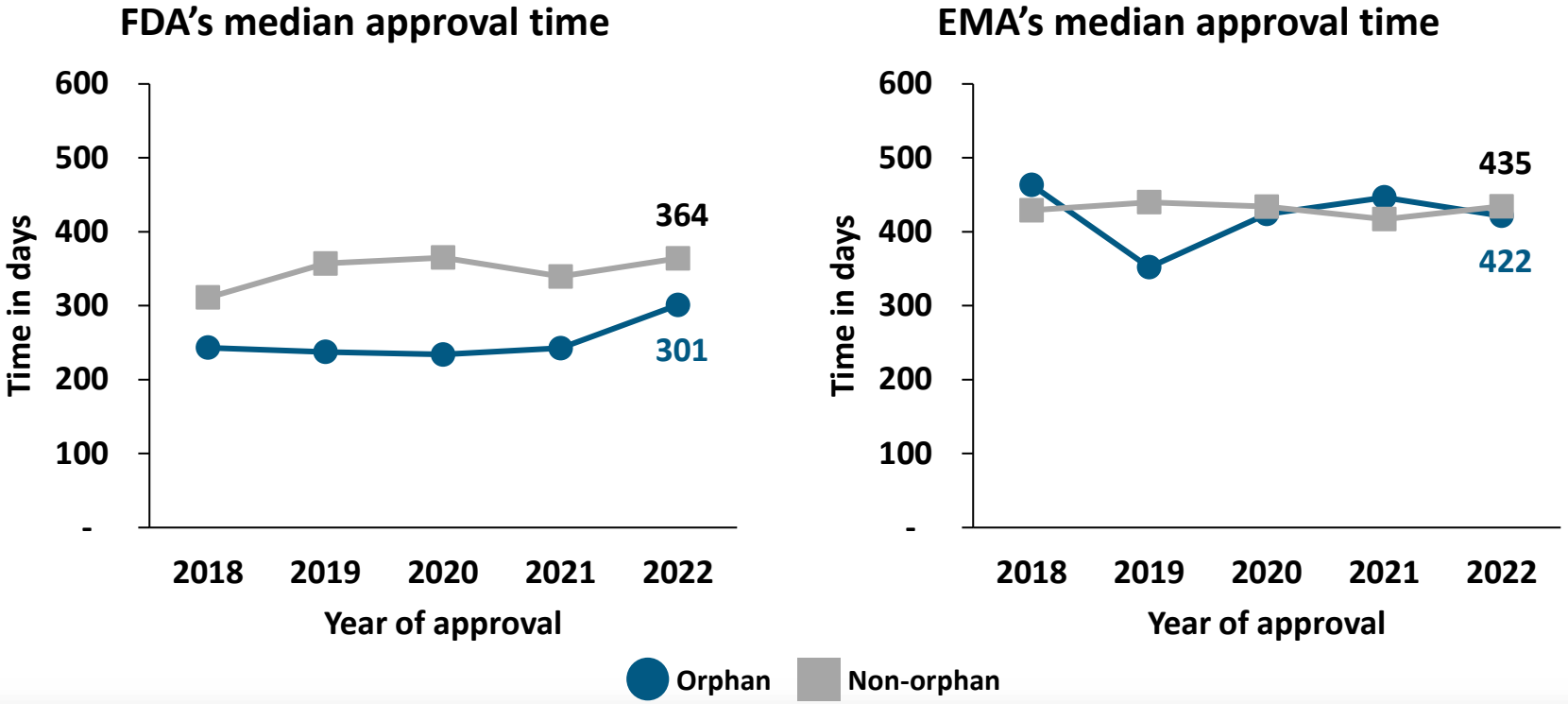


Therapeutic area distribution of orphan and non-Orphan NASs approved by the FDA and EMA between 2018 and 2022



Further analyses e.g., by year can be developed

Median approval times of orphan and non-orphan NASs approved by FDA and EMA over the last five years (2018-2022)



Approval time is calculated from the date of submission to the date of approval by the agency. This time includes agency and company time.

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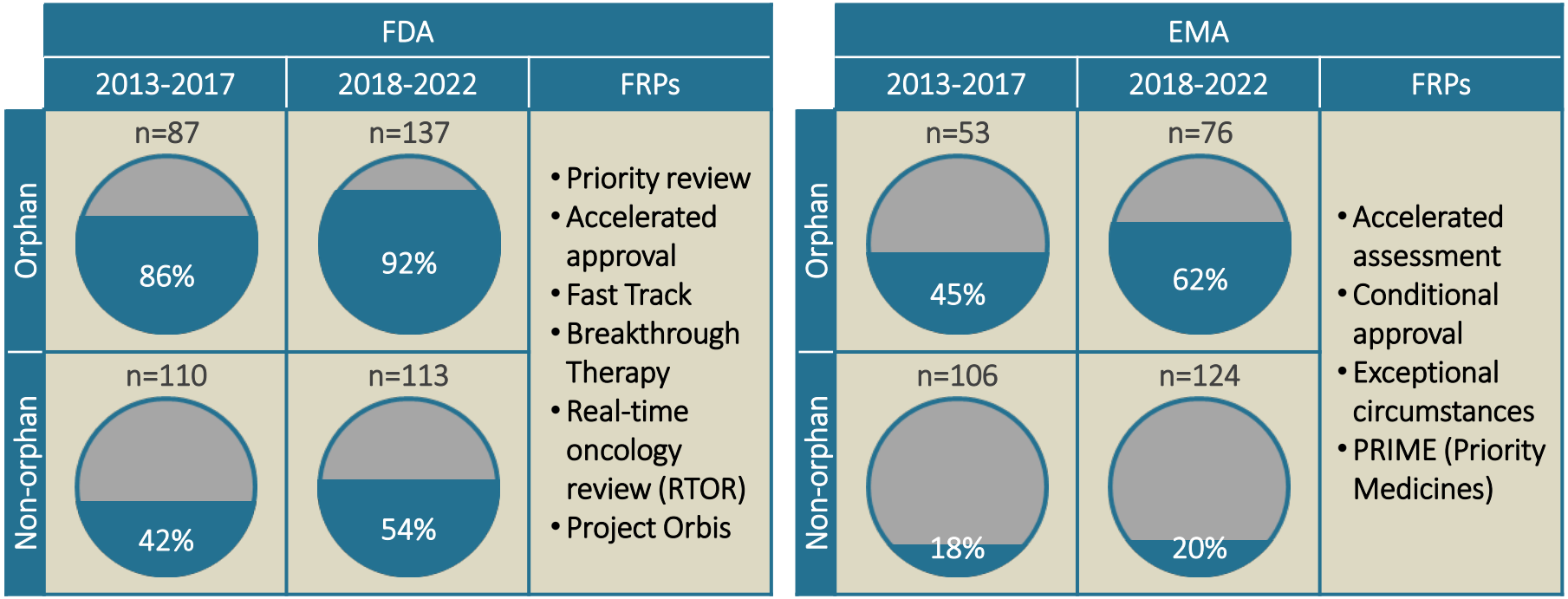
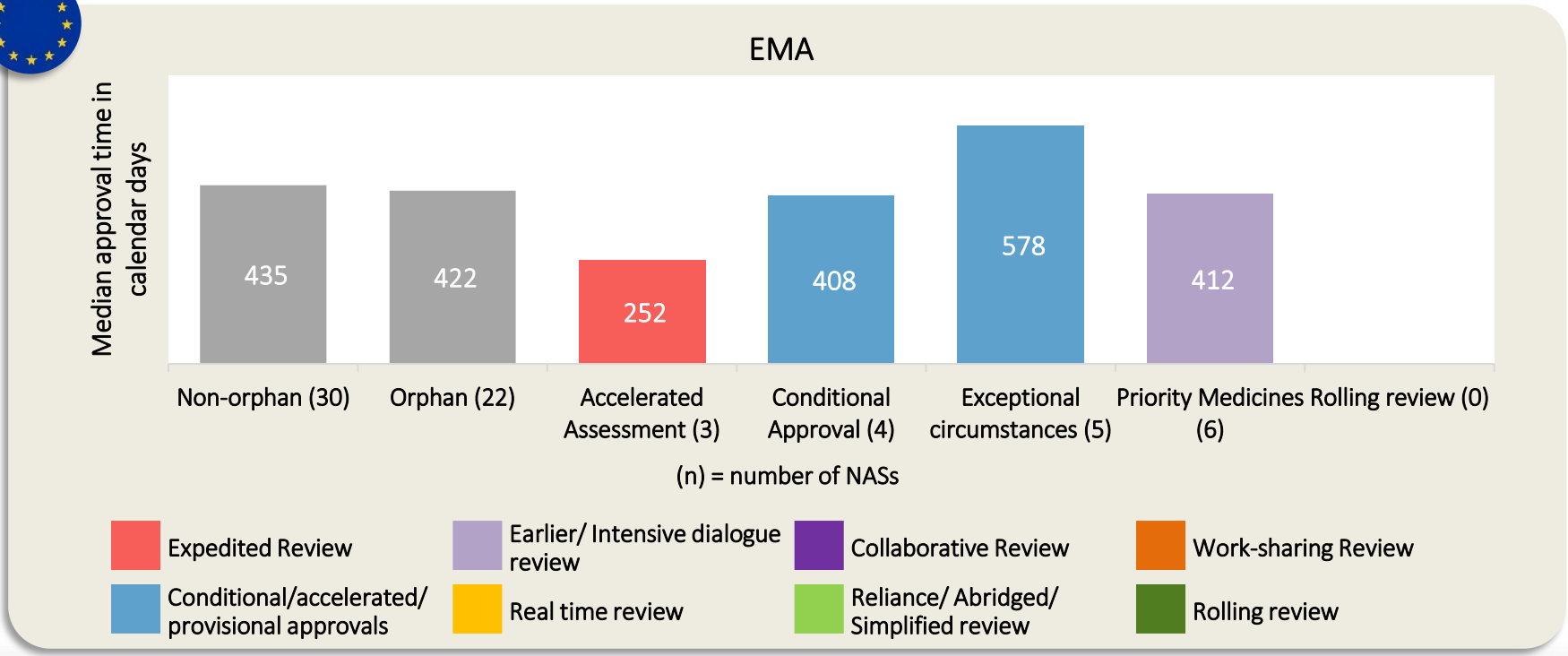
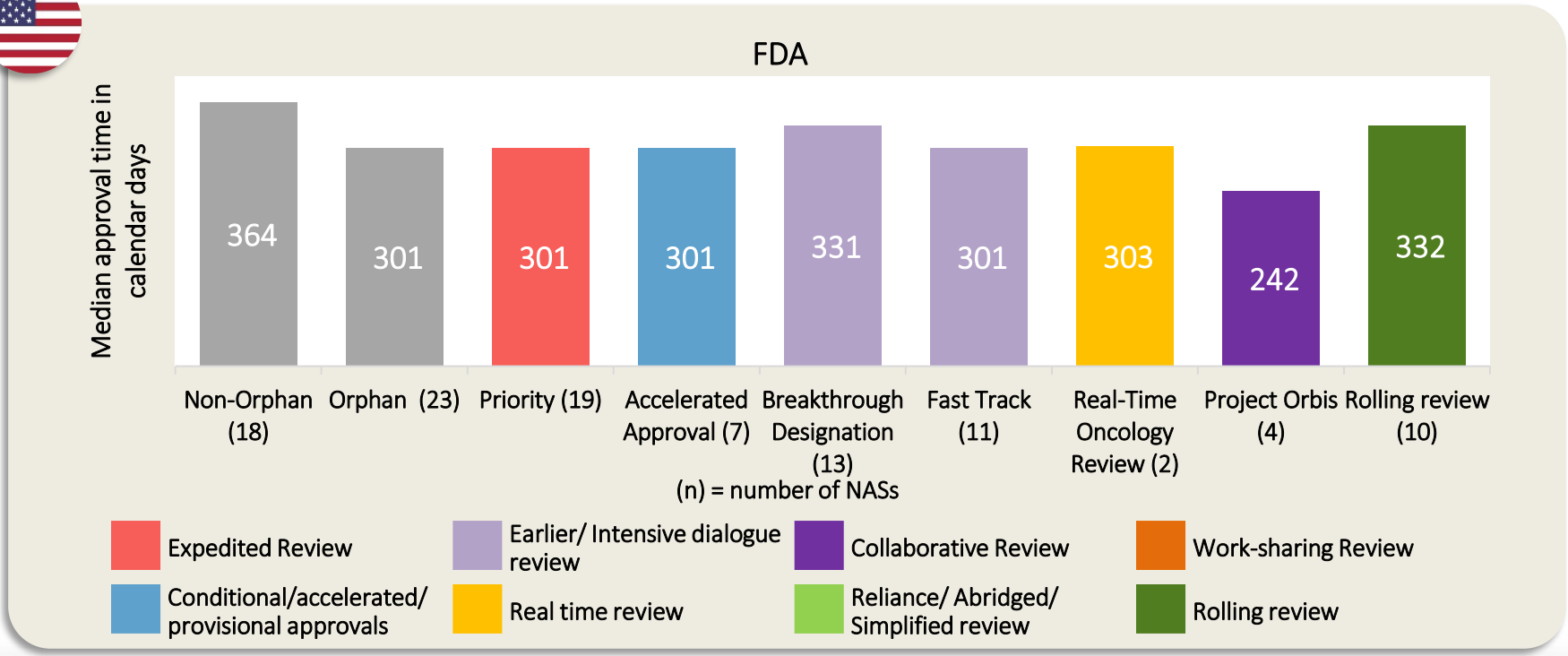
Proportion of NASs approved by FDA and EMA between 2013-2022 where at least one facilitated regulatory pathway (FRP) was used for the approval



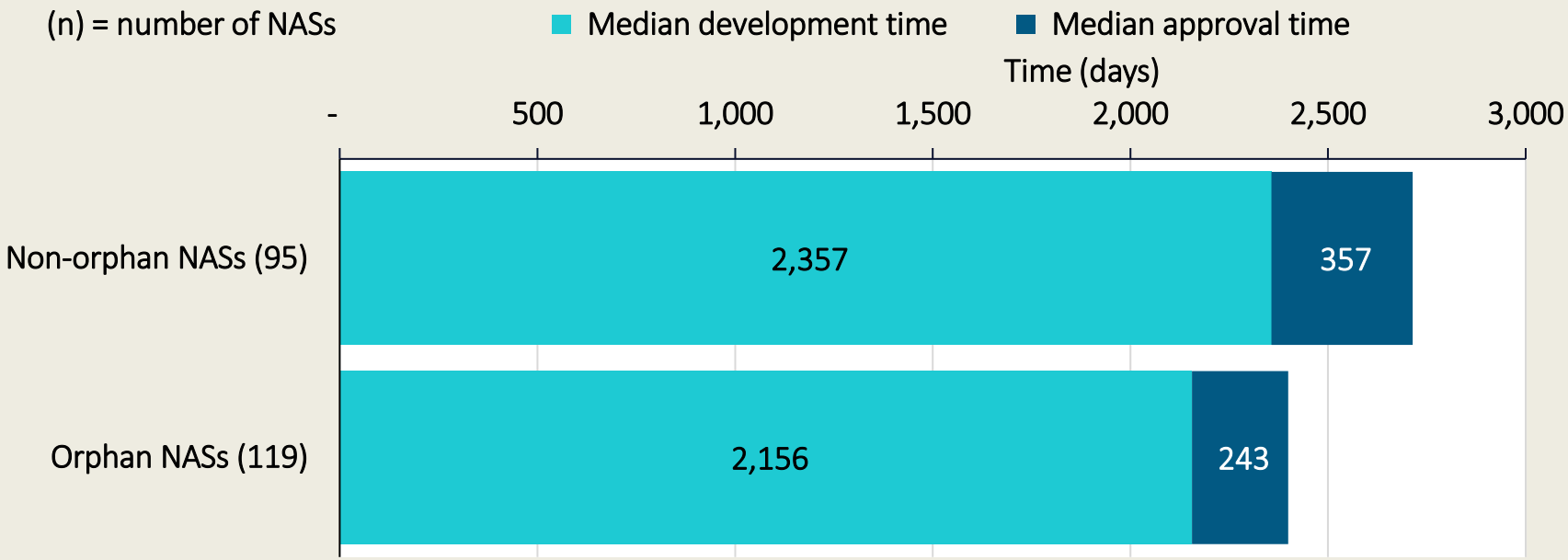
FRPs timelines of EMA — Focus on orphan NASs approved in 2022



FRPs timelines of FDA — Focus on orphan NASs approved in 2022

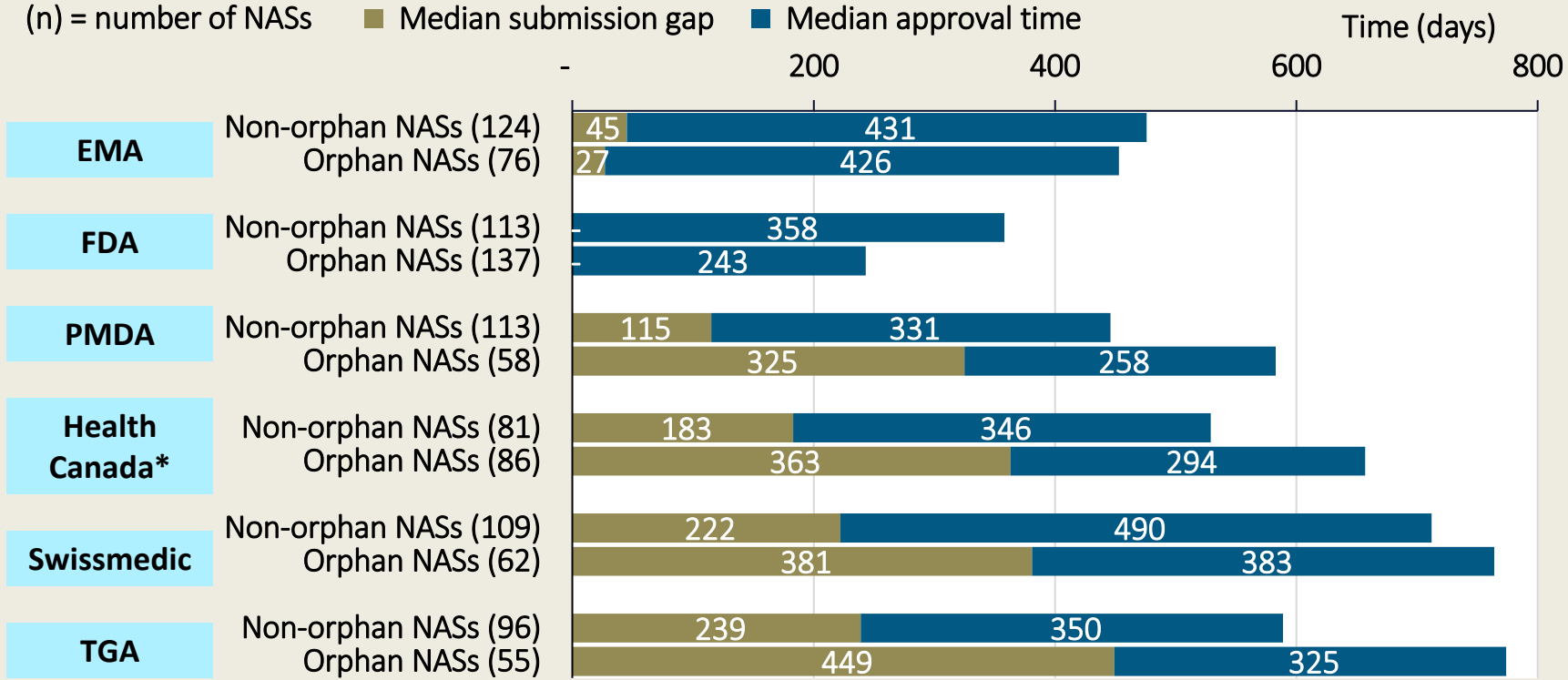


Median development and approval times of orphan and non-orphan NASs approved by the FDA between 2018 and 2022



Development time is calculated as the time from the date of approval or submission of the Investigational New Drug (IND) application to the date of regulatory submission of the New Drug Application (NDA) or Biologics License Application (BLA) to FDA. Approval time is calculated from the date of submission to the date of approval by the agency. This time includes agency and company time.

Median submission gap and approval times of orphan and non-orphan NASs approved by six agencies between 2018-2022



Submission gap is calculated as the time from the date of submission at the first regulatory agency to the date of regulatory submission to the target agency. Approval time is calculated from the date of submission to the date of approval by the agency. This time includes agency and company time. EMA approval time includes the EU Commission time.

** Health Canada does not currently have an orphan policy; this data shows the number of medicines that were approved by Health Canada that were classified as orphan by either FDA, EMA or TGA.*

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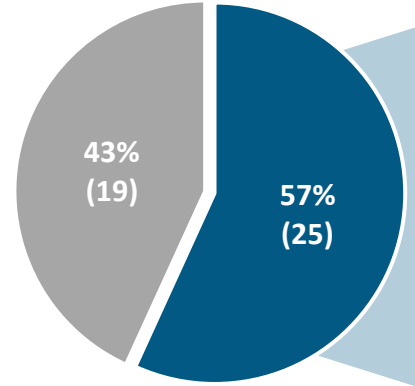
Orphan designation of NASs approved by all five agencies between 2018-2022

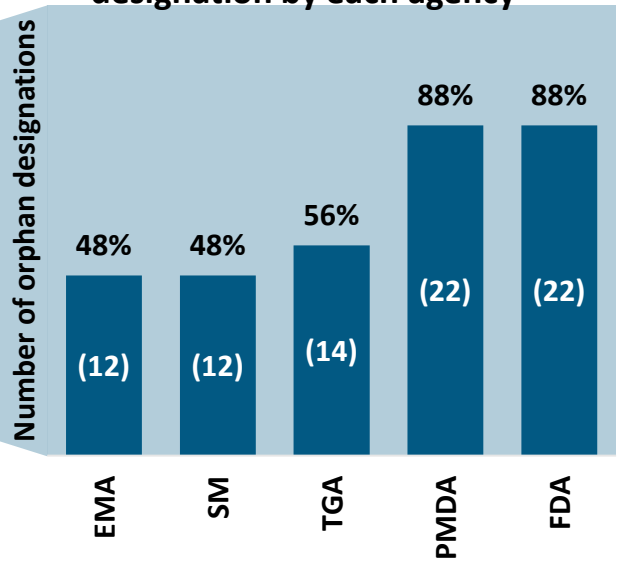
of NASs approved by all agencies*



- Orphan designation in at least one agency
- Not designated

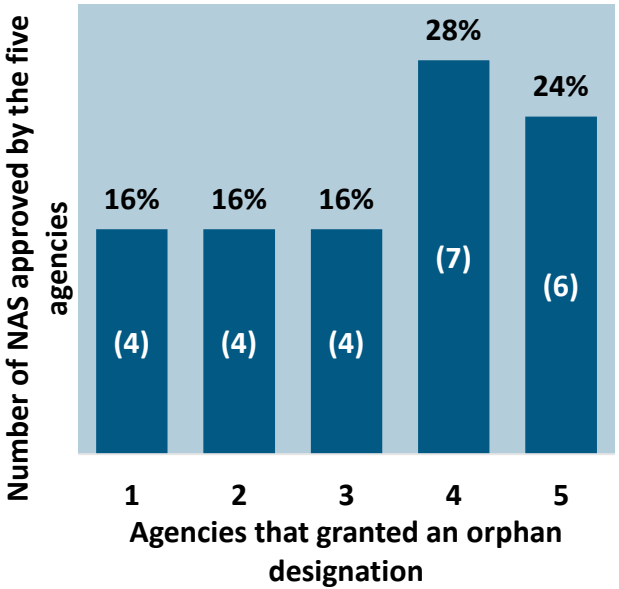
*: Not including Health Canada

Proportion of the 25 NASs granted with an orphan designation by each agency



(n) = number of NASs

Commonality of orphan designations across the five agencies



Alignment in FDA and EMA decision making

- Study to determine if EMA and FDA are aligned n their regulatory outcomes – approval decision, use of orphan, facilitated regulatory pathways, timelines
- Key findings
  - General agreement between EMA and FDA conditional approval
  - Review times faster at FDA due to use of priority review
  - 20% more frequent use of orphan designation by FDA
  - 73% concordance in approved indication (where the same indication was submitted)
- Future work - Rationale for divergent decisions?

Open access Original research

BMJ Open

To what degree are review outcomes aligned for new active substances (NASs) between the European Medicines Agency and the US Food and Drug Administration? A comparison based on publicly available information for NASs initially approved in the time period 2014 to 2016

Thomas Christian Kühler ,[1] Magda Bujar,[2] Neil McAuslane,[2] Lawrence Liberti[2]

To cite: Kühler TC, Bujar M, McAuslane N, *et al*. To what degree are review outcomes aligned for new active substances (NASs) between the European Medicines Agency and the US Food and Drug Administration? A comparison based on publicly available information for NASs initially approved in the time period 2014 to 2016. *BMJ Open* 2019;**9**:e028677. doi:10.1136/bmjopen-2018-028677

► Prepublication history and additional material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2018-028677).

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Check for updates

For numbered affiliations see end of article.

Correspondence to
Professor Thomas Christian Kühler;
thomas.kuhler@sanofi.com

ABSTRACT

Objective To compare review outcome alignment between European Medicines Agency (EMA) and US Food and Drug Administration (FDA) for medicines approved by both agencies in the time period 2014–2016.

Design Using publicly available information from FDA and EMA websites, new active substances (NASs) approved by each agency from 2014 to 2016 were identified and their characteristics assessed. Divergences in regulatory outcomes for simultaneous (within 91 days) submissions to both agencies were identified and then examined for use of facilitated regulatory pathways and orphan designations; submitted versus approved indications; and approval times.

Results In 2014–2016, 115 NASs were approved by EMA or FDA or both; 74/115 were new chemical entities and 41 new biological/biotechnology entities; 82/115 were approved by both agencies, 24 only by FDA and nine only by EMA. Simultaneous submission occurred for 52/115; 13/52 received expedited review by both agencies and 18 only by FDA; 8/52 received conditional approval from both agencies, 2/52 only from FDA and 1/52 only from EMA; 17/52 were designated as orphans by both agencies and 10/52 by FDA only; 31/52 indications were approved as submitted and 21 changed by EMA and 29/46 were approved as submitted (six not assessed) and 17/46 changed by FDA. Median FDA review timelines were 319 days compared with 409 days for EMA.

Conclusions There was general agreement in EMA / FDA conditional approvals. FDA used expedited pathways and orphan designation more often than EMA, suggesting stricter EMA criteria or definitions for these designations or less flexible processes. Despite consistency in submitted indications, there was lack of concordance in approved indications, which should be further investigated. FDA review times are faster because of a wider range of expedited pathways and the two-step EMA process; this may change with recent revisions to EMA accelerated assessment guidelines and the launch of Priority Medicines.

Strengths and limitations of this study

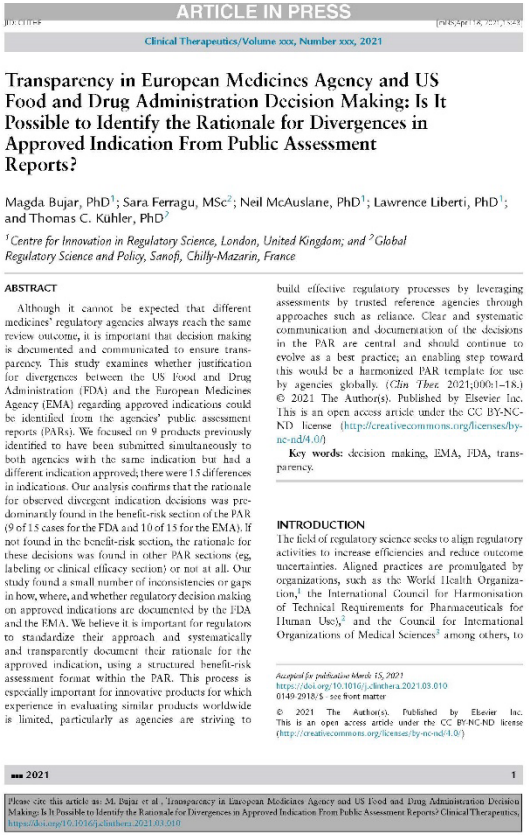
- A 91-day time window was applied to identify 'similar dossiers' being submitted to the European Medicines Agency (EMA) and the Food and Drug Administration (FDA); some uncertainty regarding the identical content could arise but it is unlikely that significant new data would be included in this short time frame.
- Extraction of publicly available data was performed using a predetermined algorithm for each variable; an independent data review was performed by each author, and discrepancies were addressed by consensus.
- Specific inclusion and exclusion criteria were used in the selection of New Active Substances allowing for a consistent cohort for comparisons across agencies.
- Redactions by the FDA in indication information necessitated the exclusion of a few compounds from comparison of submitted and approved indications.
- The lack of concordance between EMA and FDA approved indications compared with submitted indications was not studied but requires further investigation.

INTRODUCTION

The plethora of regulations that govern modern drug development and life cycle management activities across different regulatory jurisdictions has been suggested to contribute to the barriers to the delivery of

Transparency in FDA and EMA decision making

- Study to analyse divergent regulatory outcomes and whether it is possible to understand the rational based on agency public assessment reports
- For most if products, the rationale for divergences was found in the PARs
- A more systematic standardised approach to benefit-risk communication should be used
- A harmonized PAR could facilitate public trust and promote regulatory reliance
- NOTE: This work has not been updated more recently



ARTICLE IN PRESS

Clinical Therapeutics/Volume xxx, Number xxx, 2021

Transparency in European Medicines Agency and US Food and Drug Administration Decision Making: Is It Possible to Identify the Rationale for Divergences in Approved Indication From Public Assessment Reports?

Magda Bujar, PhD[1]; Sara Ferragu, MSc[2]; Neil McAuslane, PhD[1]; Lawrence Liberti, PhD[1]; and Thomas C. Kühler, PhD[2]

[1] *Centre for Innovation in Regulatory Science, London, United Kingdom; and* [2] *Global Regulatory Science and Policy, Sanofi, Chilly-Mazarin, France*

ABSTRACT

Although it cannot be expected that different medicines' regulatory agencies always reach the same review outcome, it is important that decision making is documented and communicated to ensure transparency. This study examines whether justification for divergences between the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) regarding approved indications could be identified from the agencies' public assessment reports (PARs). We focused on 9 products previously identified to have been submitted simultaneously to both agencies with the same indication but had a different indication approved; there were 15 differences in indications. Our analysis confirms that the rationale for observed divergent indication decisions was predominantly found in the benefit-risk section of the PAR (9 of 15 cases for the FDA and 10 of 15 for the EMA). If not found in the benefit-risk section, the rationale for these decisions was found in other PAR sections (eg, labeling or clinical efficacy section) or not at all. Our study found a small number of inconsistencies or gaps in how, where, and whether regulatory decision making on approved indications are documented by the FDA and the EMA. We believe it is important for regulators to standardize their approach and systematically and transparently document their rationale for the approved indication, using a structured benefit-risk assessment format within the PAR. This process is especially important for innovative products for which experience in evaluating similar products worldwide is limited, particularly as agencies are striving to build effective regulatory processes by leveraging assessments by trusted reference agencies through approaches such as reliance. Clear and systematic communication and documentation of the decisions in the PAR are central and should continue to evolve as a best practice; an enabling step toward this would be a harmonized PAR template for use by agencies globally. (*Clin Ther.* 2021;000:1–18.)

Key words: decision making, EMA, FDA, transparency.

INTRODUCTION

The field of regulatory science seeks to align regulatory activities to increase efficiencies and reduce outcome uncertainties. Aligned practices are promulgated by organizations, such as the World Health Organization,[1] the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use),[2] and the Council for International Organizations of Medical Sciences[3] among others, to

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0149-2918/$ - see front matter

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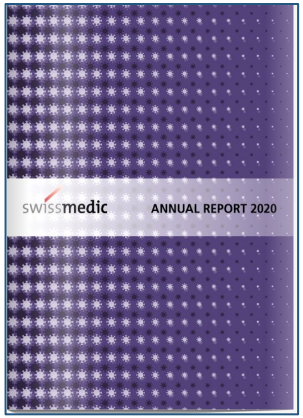
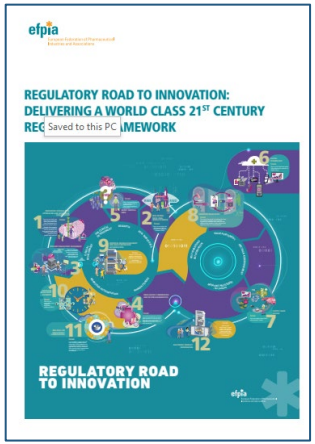
CIRS data – research, policy and advocacy

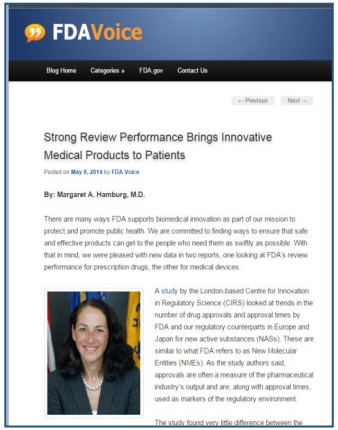
TGA and Swissmedic Annual reports



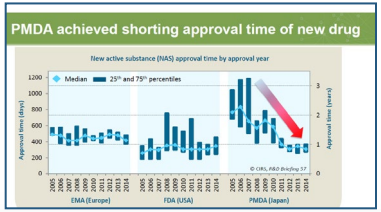
EFPIA report



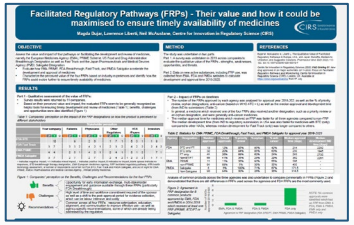
FDA Voice blog by Margaret Hamburg



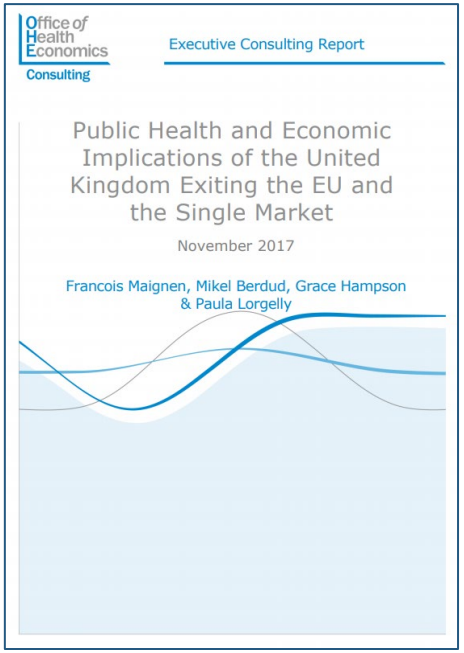
PMDA DIA presentation



CIRS DIA poster



OHE report: UK Brexit scenarios



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03 CIRS October Workshop on rare diseases - recommendations

04 Data availability within CIRS and opportunities

CIRS Workshop – October 2023, UK - Do development, review and reimbursement frameworks need adapting to improve evidence generation and financially sustainable access for rare disease products?

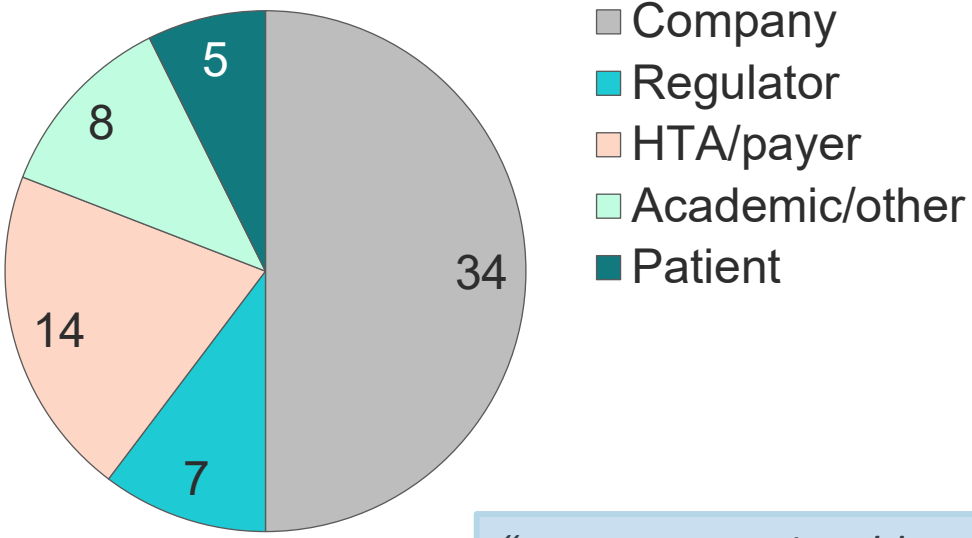
Objectives:

- Identify the perspectives from the different stakeholders on the challenges and opportunities for adapting or improving regulatory or reimbursement frameworks for rare disease products.
- Discuss how best to align evidence generation during development to meet the different needs of regulators, HTA and payers that enables decision making at the time of review and reimbursement.
- Recommendations on how best to support evidence generation, particularly focused on regulatory, HTA and payer needs to address uncertainty at the time of decision so as to enable greater patient access to rare disease products.

Output

- Slides and summaries available to members and participants
- Summary report will be available on the CIRS website in 2023

CIRS Workshop – October 2023, UK - Do development, review and reimbursement frameworks need adapting to improve evidence generation and financially sustainable access for rare disease products?



72
attendees

22
countries

4.5/5
Feedback score

"Important topic addressed by broad range of relevant stakeholders. The very high CIRS standard is being maintained in the virtual world" - HTA agency

Roundtable discussion topics

- **Policy and practice perspective -** do current incentives need to evolve for the development, review and reimbursement for rare disease?
- **Evidence development for regulators and health technology assessors** for rare disease products – how best to address (align and integrate) the needs of regulators and HTA?
- **Utilising a life cycle approach for rare disease products** to manage clinical uncertainties due to small patient populations - What are the post approval considerations for HTA, regulators and payers?

Q1: What are the key current incentives for rare disease development, review, reimbursement and ongoing evidence generation – how are they perceived – fit for purpose or could/need to evolve? Please consider from each stakeholder perspective

Current incentives	Area of incentive	Fit for purpose or could evolve –	Comment
Tax incentive for clinical R&D	Development	Could evolve	country-specific
Orphan drug designation	Review	Could evolve	Not lasting forever; may expire or may be withdrawn
User fees waived	Review	Fit for purpose	
Joint Scientific Advice	Review & Market Access	Could evolve	Not automatic currently; Should be foreseen early in process ; Criteria for eligibility
Expedited Regul. Pathways (Conditional/ Accelerated approvals, PRIME)	Review	Could evolve	Do not translate into significant benefit for HTA
Transferable Voucher	Review		Specific in certain regions (e.g. US)
Market exclusivity	Review & Economic	Could evolve	Subject to revision in new EU proposed legislation (more challenges) + country-specific
Incentives for reimbursement (Accelerated reimbursement funds)	Reimbursement	Could evolve	country-specific: different in each country => complex

Q2, 3 Are there additional or new incentives/approaches that are needed? What needs to be considered to support the evolution of incentives?

- Change terminology “incentive” e.g. “supportive measures to encourage R&D in diseases affecting small population”
- Expand toolbox e.g. Look at incentives for oncology
- Holistic methodological incentive approach across whole lifecycle: development/approval/reimbursement
- Idea of specific supportive mechanisms for making products available in middle/low income countries? (WHO Medicines Patent Pool – MPP)
- Better understanding/overview various HTA/payer and reimbursement incentives across various countries.
- Different incentive model for ultra-rare diseases ?

Selected recommendations

Recommendations (inc future work): Improving predictability for all stakeholders	Who should be involved in implementing
Improving predictability from industry perspective: • Concern: Regul. “incentives” have become “rewards” (i.e. being reassessed at the end) • To be analysed: Have current pathways (e.g. joint SA, PRIME, AA) helped improve predictability? • How to foster multistakeholders dialogue at early stage in development?	CIRS (analysis)
Improving predictability from HTA perspective: • HTA data requirements : need for early consensus on what data need to be collected and how to coordinate collection process • Cross-orphan product analysis on how HTA data assessment was conducted • Collaborative centralised data collection + analysis: idea of settig up sandbox approach for data collection and analysis	All stakeholders CIRS (analysis)
Risk mitigation from Payers perspective: • Analysis across contracts on market entry agreements	CIRS (analysis)
Improve predictability for patients: • Cross-border access to patients: Supply chain and Distribution / incl. info in their own language	Industry & Regulators (?)

Agenda

01 Introduction to CIRS and work in rare diseases

02 CIRS data – trend analysis on rare diseases including use of facilitated regulatory pathways and divergent decisions

03 CIRS October Workshop on rare diseases - recommendations

04 Data availability within CIRS and opportunities

Data availability within CIRS - Product characteristics

New Active Substances; Approval 1998-2023

- Generic name
- Brand name
- Company name
- Type of compound - Chemical Entity/Biotechnology Product/Biological
- WHO ATC code (3 letter)
- Therapeutical indication – since 2015
- Use of facilitated regulatory pathways – e.g. EMA and FDA
    - FDA Accelerated approval/ EMA Conditional/Exceptional
    - FDA Priority review/EMA accelerated assessment
    - FDA Breakthrough/Fast track/EMA PRIME
    - Rolling review
    - Project Orbis

New ways of working:

- Use of real world data
- FDA Patient experience data

Data availability within CIRS – Review timelines

- Pre-submission date
- Date of submission
- Date of receipt of dossier
- Date of acceptance to file
- Date of the start of the scientific assessment
- Date of the end of the scientific assessment
- Date of the advisory committee review
- Date of the outcome letter
- Date of the response from the sponsor
- Additional review cycles
- Date of completion of all scientific assessments
- Date of the notification of final decision
- Date of approval

- FDA - specific
  - Date of the End-of-Phase 2 meeting in FDA
  - Date of the FDA IND
  - Date of the FDA Breakthrough Therapy designation

- EMA - specific
  - Date of the EMA PRIME designation

Further analysis - metrics

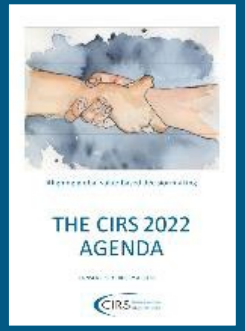
- Development time – use of scientific advice, facilitated pathways
- Orphan designation – how much is it used for rare diseases vs stratified common disease
- Rationale for divergence in designation – requirements vs company strategy
- Regulatory outcome – comparison of indications approved by EMA/FDA and alignment

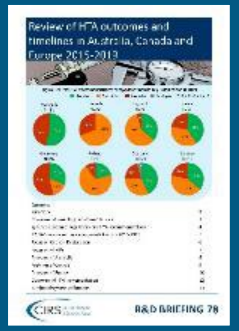
Additional suggestions for future research

- Comparison of regulatory processes and pathways used to enable rare diseases drugs – development, review, reimbursement
- A mapping of definitions and requirements across agencies
- Incentives for rare diseases – analysis of those and best practice; impact on company strategy

THANK YOU!

Download our latest publications at cirsci.org





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