Patient registries in regulatory decision-making

Regulator's vision and experiences

Patricia McGettigan

Clinical Pharmacologist

PRAC Independent Scientific Expert

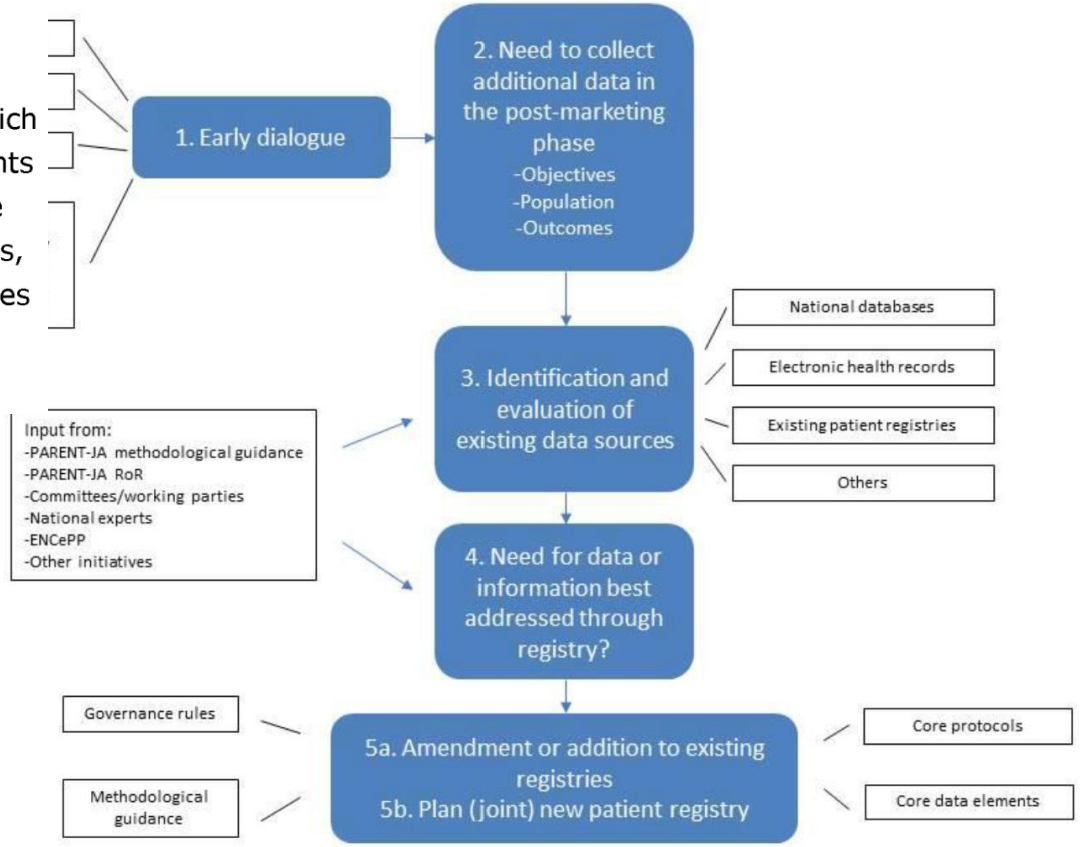
Today – regulatory perspective

- How we got here (Slides 3 - 5)
- How are we doing? (6 – 8)
- Challenges (9 – 10)
  - Registry related
  - Regulator related

with some examples as we proceed

Defining a regulatory need – Foresight
Recognising the value of real world data in regulatory evidence

The European Medicines Agency Registry Initiative is based on the recognition of the need for information across the life cycle of medicinal products in order to better understand disease characteristics and progression, to understand current clinical care and collect data on the effectiveness and safety of medicines beyond what is available from the evidence supporting the marketing authorisation. Such evidence is generally derived from randomised controlled studies, which in order to investigate efficacy, are conducted in tightly defined populations and often exclude patients in whom the medicine may be used when the product is marketed. As a result, the EMA may require the marketing authorisation applicant or holder (MAA/MAH) to provide evidence on disease outcomes, effectiveness and safety unavailable from clinical trials. There are multiple real world evidence sources of potential value, including registries, typically patient registries as defined in the EMA's Patient Registry Initiative.



December 2014: EMA Patient Registries Task Force

Patient registries are one of multiple sources of real world data that may provide evidence for regulatory decision-making

Regulator perspective
Characteristics of registry data that can provide 'useable' evidence for regulatory decision-making

- Accurate
  - Precise, reliable
- Adequate
  - Adequate range of characteristics of population covered & duration of follow-up
- Consistent
  - Across countries / data sources - or differences can be explained
- Derived from sources of demonstrable good quality
- Timely
- Valid
  - Internal and external validity

[*Sabine Straus, PRAC*]

Stakeholders
What do they need?
How can they collaborate?

Patient Registries Workshop, 28 October 2016
Observations and recommendations arising from the workshop

Report on Cystic Fibrosis Registries - Workshop 14 June 2017
Patient Registries Initiative

Report on Multiple Sclerosis Registries - Workshop 7 July 2017
Patient Registry Initiative

Report on Haemophilia Registries Workshop 8 June 2018
Patient Registries Initiative

Report on CAR T-cell therapy Registries Workshop 9 February 2018
Patient Registries Initiative

Report of the workshop on the use of registries in the monitoring of cancer therapies based on tumours' genetic and molecular features - 29 November 2019
Patient registries initiative

Report on Haemophilia Registries Workshop 8 June 2018

Patient Registries Initiative

Stakeholder 'Priority' and 'Nice-to-have' data elements

Category	Data	Already captured in at least one registry?	Priority	Frequency where applicable
Medical history	• Immune tolerance induction (ITI, yes/no)	Yes	Crucial	NA
	• Annual Bleeding Rates and subfields (traumatic/ non-traumatic)	Yes	Crucial	NA
	• Patient product preference	No	Nice to have	NA
	• Product name; Dose; Frequency of administration (only for PEGylated products)	Yes	Crucial	Annually
	• Treatment: batch and lot number for gene therapy	No, but can be retrieved if required	Crucial	NA
Immunogenicity	• Binding and Neutralising antibodies (rFVIII and rFIX including extended half-life products, PEGylated, gene therapy)	Yes	Crucial	Defined by 2 tests when detected
	• Other antibodies (anti-Mab) (only for Mab products)/ aPTT anti-PEG antibodies • Association with adverse event	No	Crucial	NA

Category	Data	Already captured in at least one registry?	Priority
	products)		
Safety reporting	• Fatalities	Yes	Crucial
	• Transmission of infectious agents (plasma-derived products)	Yes	Crucial
	• Viral vector-associated disease (gene therapies)	Yes	Crucial
	• Nephrotic syndrome (PEGylated products)	Yes	Crucial
	• Neurological events (PEGylated products)	Yes	Crucial
	• Thromboembolic events (including thrombotic micro-angiopathy)	Yes	Crucial
	• Malignancies and other potential late events	Yes	Crucial
	• All serious adverse events (AEs)	Yes	Crucial
	• New onset autoimmune events	No	Nice to have
Quality of Life data	• EQ-5D-5L	No	Crucial*
	• SF-36	No	Nice to have
	• Brief Pain Inventory Short Form	No	Nice to have
Specific data for gene therapy			
Medical history and efficacy monitoring	• Factor VIII activity (%)	No	Crucial
	• Factor IX activity (%)	No	Crucial

Product lifecycle: Opportunities to consider registry data

Start early

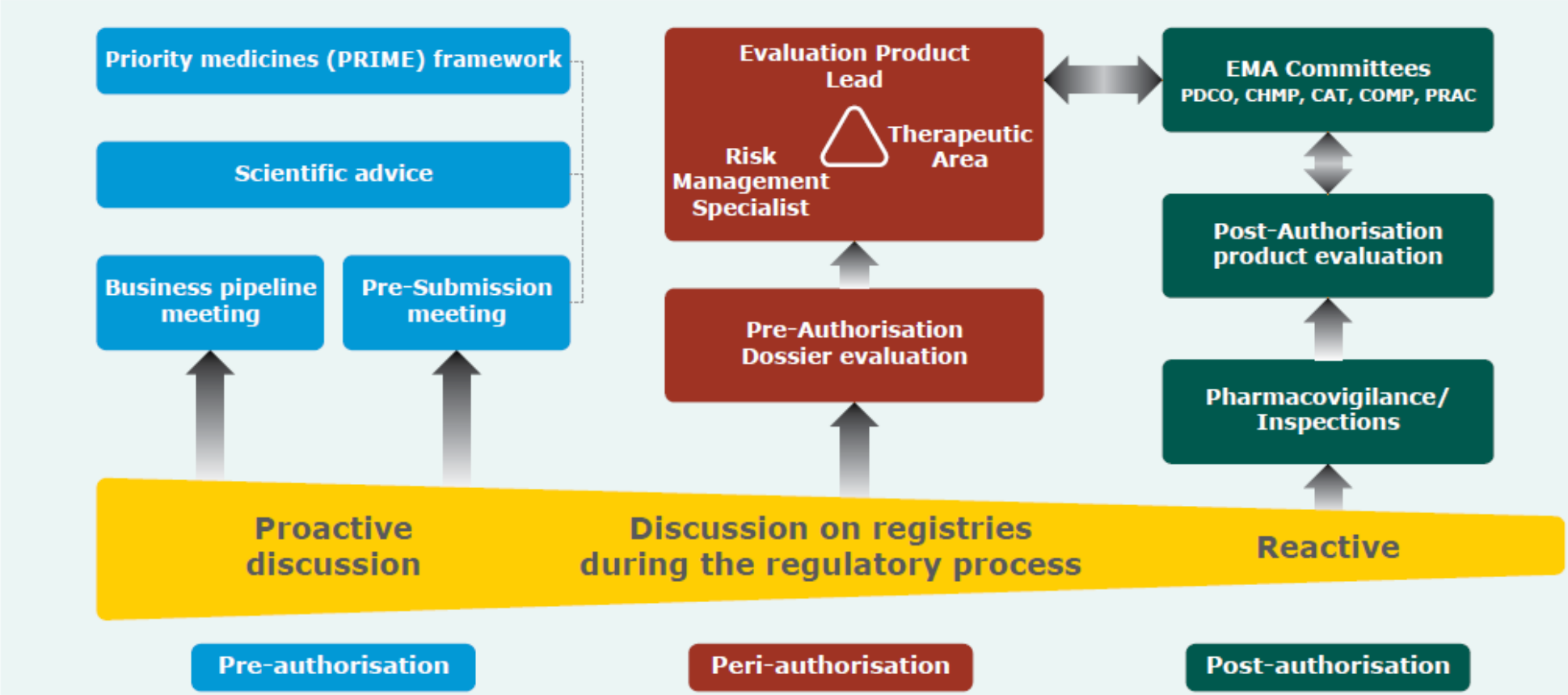


Figure 1 - Opportunities for registry consideration during the authorisation process

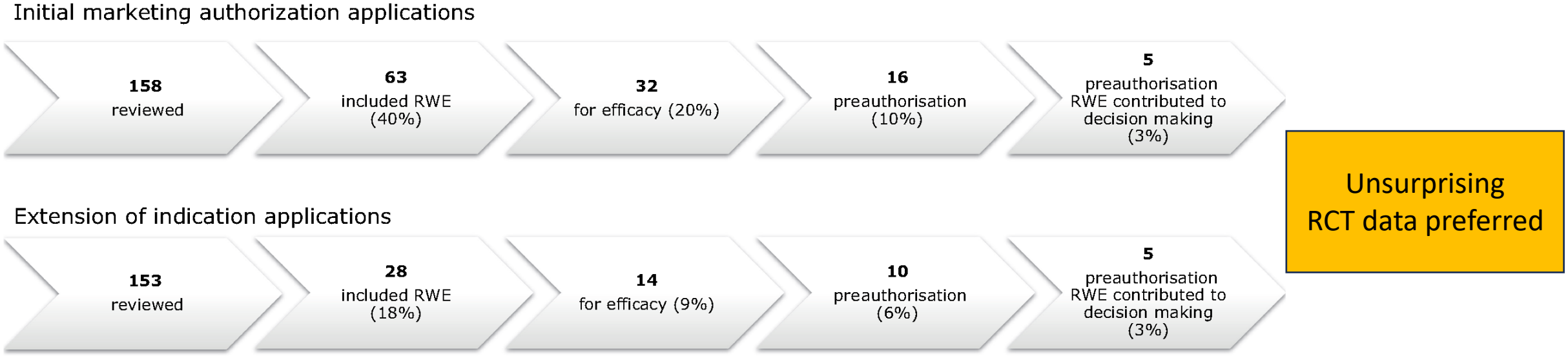
CAT: Committee for Advanced Therapies; CHMP: Committe for Medical Products for Human Use;
COMP: Committee for Orphan Medicinal Products; PDCO: Paediatric Committee; PRAC: Pharmacovigilance Risk Assessment Committee.

Marketing Authorisation Application (MAA)
Real World Evidence (RWE) of any type contributes to few MAAs

Taking two years of MAAs, 2018 – 2019: In efficacy evidence considered by CHMP

- No MA initial application was supported by registry data
- Two EoIs were supported by Registry data - rare haematological conditions
  - Glanzmann's thrombocythaenia
  - Congenital FXIII A-subunit deficiency

Bakker *et al* 2022



Registry data
Small contribution to decision-making in the context of initial marketing authorisation application (MAA)
Larger contribution in the Post Authorisation context

MAA - initial

- In evaluations of therapies for rare / uncommon conditions, many being genetic disorders, their value is evident, e.g.,
  - Haemophilia
  - Cystic Fibrosis
  - Muscle Dystrophies

Post Authorisation

- Extension of Indication (EoI)
- Evaluation of benefits / harms (PAES / PASS) associated with
  - Therapies for haemophilia, cystic fibrosis, muscle dystrophies
  - Multiple other therapies, e.g.,
    - Janus kinase inhibitors
    - Topiramate
    - Vaccines (e.g., HPV vaccines – pregnancy)

Challenges: Registry related & (some) solutions

- Data consistency, quality & availability
  - Some hopes achieved; Some registries over-optimistic – slowed regulatory use
  - Solutions: Clear Question (MAA, PASS, PAES); Examine closely the feasibility of proposals / protocols for answering the question
- Upstream system / process factors affecting registry availability / use
  - Data entry duplication is common
    - Registry is typically a separate entity from the patient healthcare record; has its own customised platform e.g., ECFS Patient Registry, BigMS, MSBase, SWEDEHEART / EuroHeart
  - Lack of registry linkage with routinely collected healthcare data & data relevant for HTA – work participation, education
    - Including for well-supported registries
  - Solutions: obvious but (prohibitively?) complex
- Registry support
  - Personnel, financial, training, time requirements to sustainably maintain comprehensive registries of acceptable quality are high
    - Consequently, some EU states' patients un-/ under-represented in some registries
  - Solutions: complex, costly?

Registries rise to challenges
Ivacaftor / tezacaftor / elexacaftor (Kaftrio)

Initial MAA

Indicated for cystic fibrosis in patients with specific gene mutations

- Registry data inadequate to inform on efficacy in genotypes

Extension of Indication

- Registry had addressed the gap by adapting genotype data collection
- Informative data were available – Registry now had genotype level data on clinical endpoints

Challenges – Regulatory 'accounting' of data supporting decision-making & (some) solutions

Currently

- No systematic recording of the nature of data that supported MAA or post-authorization evaluations
  - Assessment reports do not categorise supporting data
    - Variable terminology, e.g., 'observational data', 'non-interventional study'
    - Limitations of the data are described
    - Strengths / value of the data are omitted
- Manual searches currently to identify the nature of supporting data

Solutions

- Structured approach
  - In regulatory assessments, include a standardised summary to describe nature, contribution, strengths, limitations of supporting data
  - This would be searchable, permitting evolution of data characteristics / quality to be tracked comprehensively thereby assisting in identifying gaps, addressing these with stakeholders, recognizing both unique and common problems, devising customized & common solutions

[Bakker et al, 2022]