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Lessons from the EMA Patient Registries Initiative

STAMP Commission Expert Group
8th June 2018

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EMA Relocation: Business Continuity

Due to uncertainties on staff loss and other relocation implications, **all activities** on real world data, big data and registries between September 2018 and June 2020, will need to be prioritised in the context of **business continuity planning**

In this presentation:

- Core concepts
- EMA-imposed registries – experiences and case for the Registries Initiative
- The EMA Patient Registries Initiative - Strategy
- EMA Registry workshops – lessons learned?
- Parallel Regulatory HTA engagement
- How can regulators support use of disease registries?
- Conclusions

What are the core concepts?

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Registry

An organised system that uses observational methods to collect uniform data on specified outcomes in a population defined by a particular disease, condition or exposure.

Regulators generally prefer *patient (disease) registries* over *product registries*

- They gather insights on clinical outcomes of conditions with different treatments, rather than on the outcomes of specific treatments
- They allow comparisons
- They are generally better integrated into health care systems.

Background: EMA imposed registries

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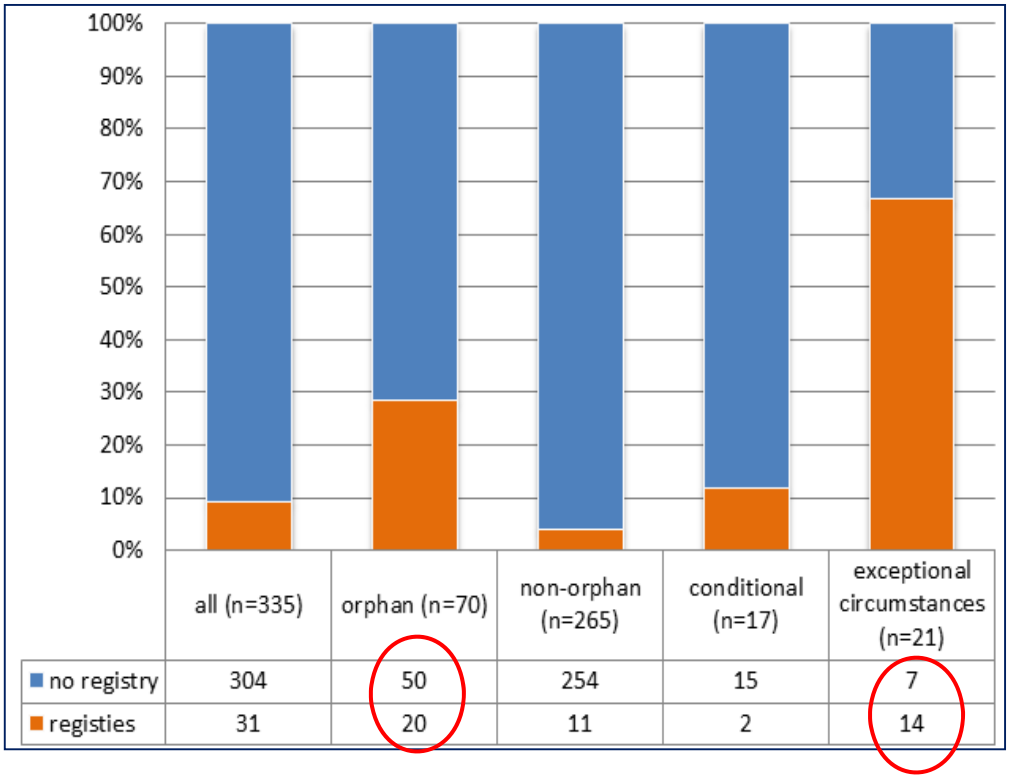
Registries may be requested of / or imposed on companies as part of risk management plans including for:

- advanced therapies
- orphan products
- medicinal products – paediatric use

Examination of registries imposed as an obligation at the time of authorisation for centrally-authorised products, 2005-2013

Overall, use of a registry imposed for 10% of products authorised

Bouvy et al. PDS 2017;26(12):1442-50 (EMA study)



	all (n=335)	orphan (n=70)	non-orphan (n=265)	conditional (n=17)	exceptional circumstances (n=21)
no registry	304	50	254	15	7
registies	31	20	11	2	14

Background: Problems observed with imposed registry studies

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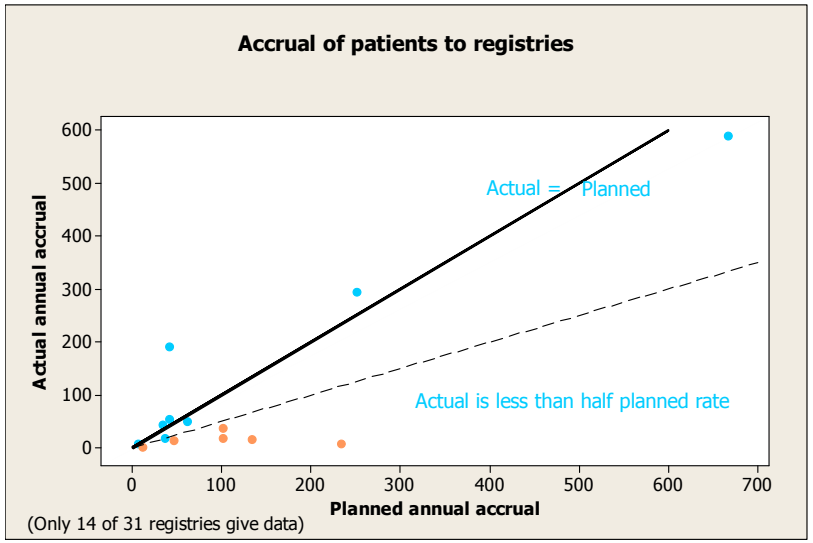
Registry issues	N (24 Total)	%
No problem reported	9	37.5
Low accrual rate	13	54.2
Delayed start	9	37.5
Protocol amendment required	9	37.5
Low quality / missing data	3	12.5
Low use of product	3	12.5
Low enrolment for other reasons	3	12.5



16/24 (66%) registries were product specific
19/24 (80%) were new registries
7 registries never commenced

Actual vs. planned number of patients included

● < 50% inclusion

Analysis of European Public Assessment Reports, study protocols, PSUR and PSUR assessment reports. Data lock: 30 June 2015

Bouvy *et al*. PDS 2017;26(12):1442-50 (EMA study)

PSUR = Periodic Safety Update Report

Reasons for problems encountered

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Approach to registries often suboptimal in scientific and resource terms:

- Existing registries not fully exploited →duplication of efforts and inefficiencies
- Discrepancy between data collected by registries and data requested by regulators

- *Existing patient (disease) registries were not set up for regulatory purposes*
- Challenges in using registries for regulatory studies:
  - **Recruitment:** lack of physician engagement due to administrative burdens, patient consent, low product usage and competing registries
  - **Data quality**: representativeness of registry population, missing data
  - Lack of consistent data **quality control**
  - **Sustainability** (funding)
- So companies may prefer to establish individual product registries

The EMA's Patient Registry Initiative

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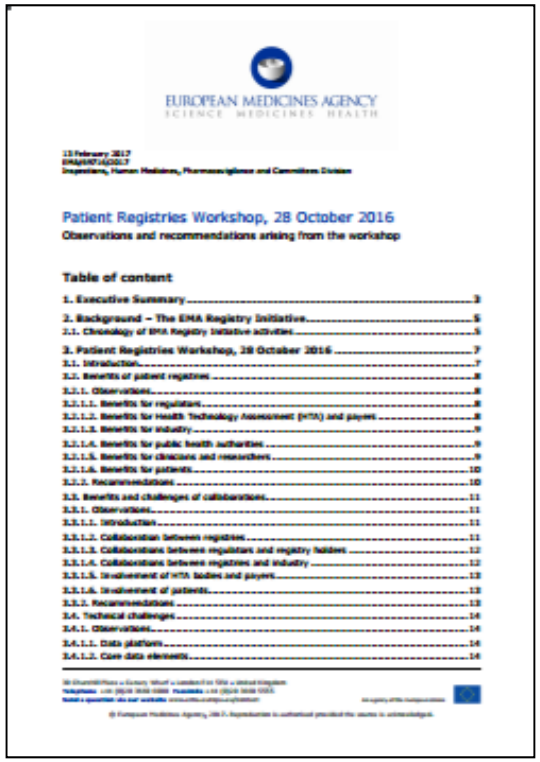
- Launched, September 2015 - Cross-Committee Task Force
- **Aims to facilitate use of patient (disease) registries by introducing and supporting a systematic approach to their contribution to the benefit-risk evaluation of medicines**
- **Pilot phase, 2016**: Stakeholder feedback encouraged an active role of EU network in supporting collaboration for greater utilisation of disease registries
- **28th October 2016 - Stakeholder workshop: focus on methods**
- **Specific workshops**
  - **June 2017: Cystic fibrosis registries**
  - **July 2017: Multiple sclerosis registries**
  - **February 2018: Registries for CAR T-cell therapies**
  - ***June 2018: Haemophilia (Factor VIII) registries***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Patient Registries Workshop, 28 October 2016

Observations and recommendations arising from the workshop

Table of content

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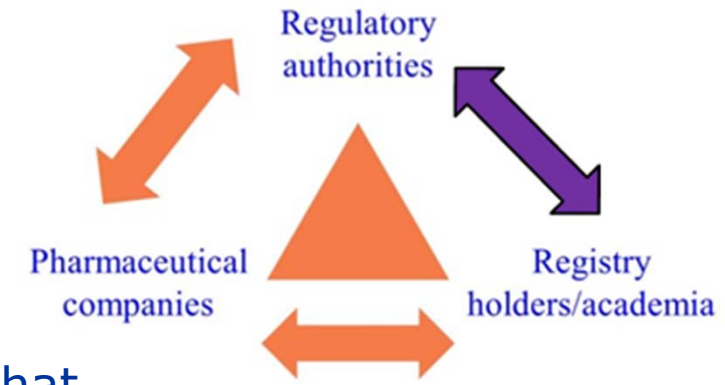
Patient Registry Initiative strategy - key components

- To promote dialogue between regulators, companies and registry holders to understand barriers and opportunities of using disease registries.



Source: Nicola Ruperto, PRINTO

- To clarify concepts: **registry vs. study** that may be registry-based

EMA registries workshops

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Cystic Fibrosis Registries Workshop: 14th June 2017

Multiple-Sclerosis Registries Workshop: 7th July 2017

CAR T-Cell therapies Registries Workshop: 9th February 2018

Participants: regulators, companies, registry holders, health technology assessment bodies, patient and health care representatives

Diseases selection?

- ✓ Products recently authorised or authorisation process ongoing
- ✓ New products - business pipeline
- ✓ EU disease registries have requested support for harmonisation
- ✓ On-going qualification procedures for two EU-wide registry platforms

EMA registries workshops

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Cystic Fibrosis Registries

Well-organised Europe-wide network; Core common data elements in place

Multiple-Sclerosis Registries

Two registry groupings: European MS Platform (patients) & Big MS Data (academic); Limited between-grouping collaboration; No within-group agreement on core common data elements

CAR T-Cell therapies Registries

European and US registry networks; Collaborative ; Data element harmonisation ongoing

Lessons learned and challenges

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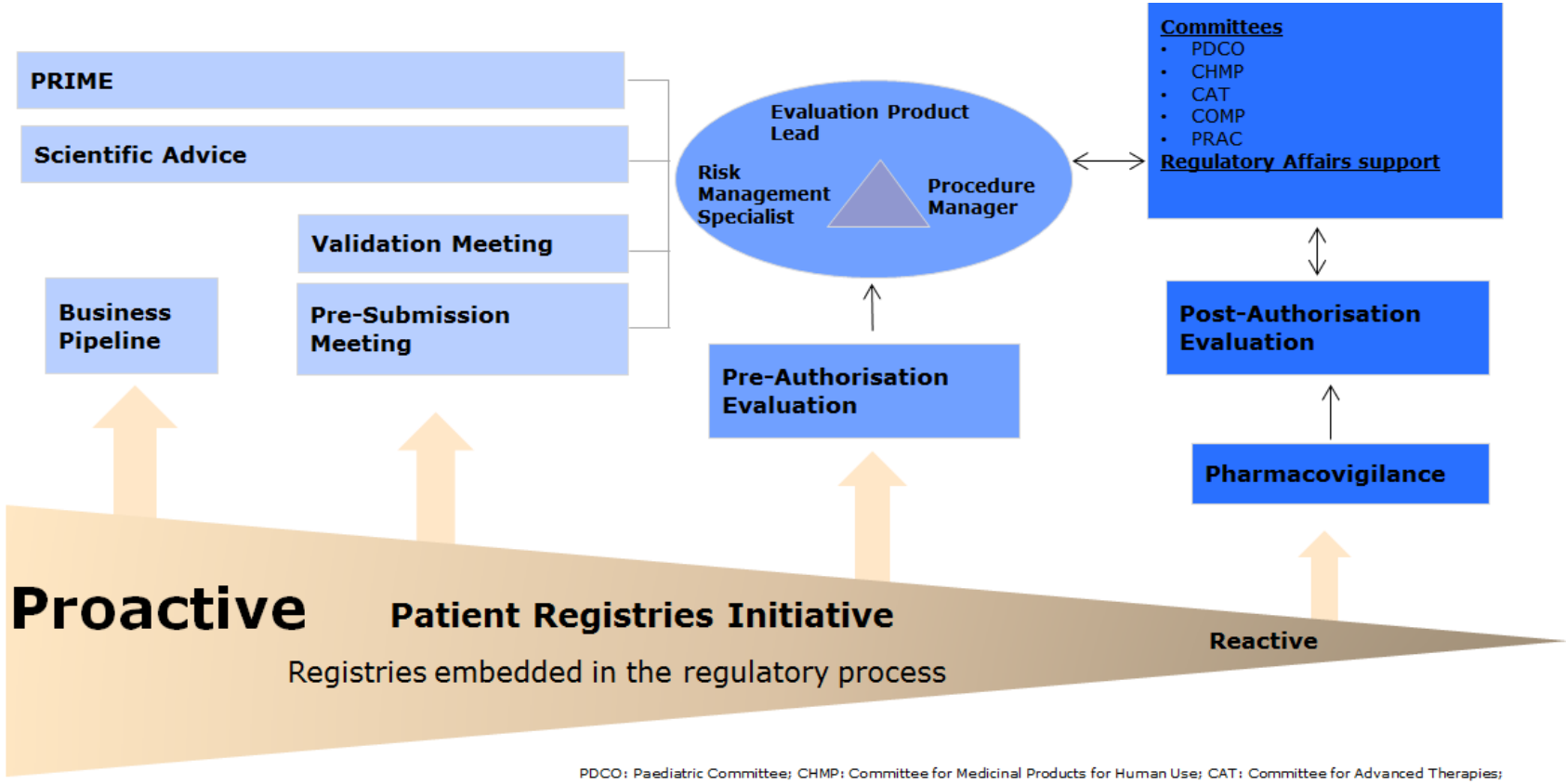
Proactive early discussion during the regulatory process



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

Lessons learned and challenges

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Governance

- **Regulators and marketing authorisation holders / applicants (MAHs/MAAs)**
  - Need to be aware of data that can feasibly be collected by registries
  - Inform registries on their data needs - early discussions
  - Process for collecting and reporting events defined / described in study protocol
- **Registry holders**
  - Consent and governance arrangements align with EU General Data Protection Regulation
  - Develop policy for timely data sharing based on data protection and informed consent
  - Establish a system for centralised data application requests
  - Require sustainable funding for registries
- **All**
  - Transparency on access to, sharing of, and publication of data

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Core common data elements

- Participants were able to agree on core data elements to be collected
- Distinction between "must have" and "nice to have" data
- Additional data can be collected if needed to support a study
  - Needs early discussion, flexibility, agreement, registry lead-in time
  - Marketing authorisation applicants need to commit time / personnel long before approval
  - **Care**: More data ask = more registry workload & risks lower quality data

Lessons learned and challenges

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Data Quality

Recurrent concern for registry holders, MAHs/ MAAs and regulators

- Key components of quality:
  - Uniformity, representativeness, consistency, completeness, accuracy, timeliness
- Source data verification procedures needed
- Data quality control system to be established internally
- External audit to be considered
- Data quality indicators to be defined
- Similar data quality in routine collection and in registry-based studies

Parallel Regulatory HTA engagement in discussions on Post-Licensing Evidence generation

HTA Network (HTAN) reflection paper and HTAN synergy group

EMA - EUnetHTA bilateral meetings

Parallel Qualification of registries and parallel product advices

EMA research and development platform, and Focus group

Exploring HTA-Regulatory synergies: Call on a strategic level

HTA NETWORK REFLECTION PAPER ON "SYNERGIES BETWEEN REGULATORY AND HTA ISSUES ON PHARMACEUTICALS"

ADOPTED BY THE HTA NETWORK, 10 NOVEMBER 2016

a) Pre-marketing phase

b) Market Entry

c) Post Marketing - Real world effectiveness and safety

The Ad-hoc Synergy Group with HTA representatives (i.e. HTA Network and EUnetHTA JA3) and regulators (i.e. STAMP, HMA, EMA) is currently mapping the actions.

Engagement through the EMA/EUnetHTA work plan 2017-2020

"Late dialogues" / peri-licensing advice	
Gaining experience with peri-licensing advice on post-licensing data generation plans with a focus on specific products (e.g., ATMPs) or regulatory processes or tools (e.g., CMA, Adaptive Pathways, or PRIME)	Provision of parallel consultation on requirements for post-authorisation data collection plans (including registries)
Optimise utilisation of post-licensing evidence generation for decision making	Collaboration in requirements for data collection and analysis of real world data including registries

Website

Parallel procedures in RWD settings

Qualification procedures assess the potential fitness of data derived from registry for specific types of study objectives in regulatory decision making

ECFSR registry

- HTA substantive participation as individual HTA bodies (3); also HTA observers (4)
- CHMP opinion re registry use. HTA advices drafted

EBMT registry (CAR-T) data requirements

- CHMP drafting opinion re registry use. Products under MAA simultaneously.
- HTA observers only (6+ EUnethTA); products not yet under reimbursement appraisal

Parallel advice procedures

- Post authorisation safety study protocol for product; EUnetHTA observer
- Use of RWD in post Conditional Marketing authorisation setting to expand safety and effectiveness data; HTA participation substantive as individual HTA bodies (5)

EMA research and development platform with Industry associations

EMA research and development platform with Industry associations; fully transparent/ published report and presentations

Website

Discussion on Post licensing evidence generation (PLEG)advices at 2nd meeting

- EMA
- EUnetHTA rep invited to co-present
- Outcome Focus group (EMA, Industry and EUnetHTA rep) for greater in depth understanding of barriers and issues to seeking advice on PLEG

Learnings re Regulatory HTA engagement in post-licensing evidence generation

- Issues and barriers for different stakeholders in participating in PLEG advices need to be understood, be transparently & widely communicated, and addressed
- Exchange of information on processes, tools and workshops needs to continue through relevant and appropriate fora
- Foundation on which to build process for rationale PLEG evidence generation to benefit public health

How can regulators support use of disease registries?

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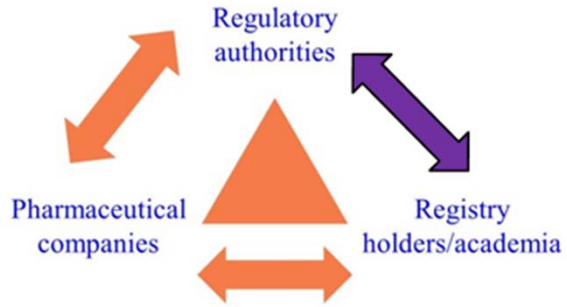
- **Methodological guidance** on use of disease registries from a regulatory perspective: Likely consultation 2018
  Will address regulatory requirements and guidance for collecting / reporting AEs and ADRs
- **Scientific Advice** on PASS/PAES study protocol using registries, e.g. joint collaborative studies (involve HTA and payers where possible)
- **Inventory of disease registries** - ENCePP Resources database, www.encepp.eu
- **Facilitation of interactions** between regulators, industry and registry holders during the entire life cycle of a product
- **Collaboration with EU initiatives**, e.g., EUnetHTA Joint Action 3, EC JRC European Platform on Rare Disease Registration



EMA Qualification procedure

A voluntary scientific pathway leading to a Committee for Medicinal Products for Human Use (CHMP) opinion or a Scientific Advice on innovative methods or drug development tools

CHMP qualification opinion on the European Cystic Fibrosis Society Patient Registry

- Its current status may allow its use as a data source for regulatory purposes in studies of drugs authorised for CF (Secondary use)
  - Drug utilisation studies
  - Drug efficacy / effectiveness studies
  - Drug safety evaluation

http://www.ema.europa.eu/ema/index.jsp?curl=pages/includes/document/document_detail.jsp?webContentId=WC500243542&mid=WC0b01ac058009a3dc

How can regulators support use of disease registries?

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* Qualification procedure

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1 Procedure No.: EMEA/H/SAB/080/1/QA/2017
2 EMA/CHMP/SAWP/802259/2017
3 Product Development and Scientific Support Department

4 Qualification Opinion

5 The European Cystic Fibrosis Society Patient Registry (ECFSPR)

23 Published for consultation on the EMA website; Consultation closed 9th April 2018

Conclusions

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- Paradigm shift from "product registry owned by single company" to "(joint) collaboration with disease registry for long-term patient follow-up"
- Concerns about data quality of existing disease registries but workshops demonstrated companies and registry holders are agreeable to collaborate
- Gap between the amount/type of data collected in disease registries and data requested by regulators
    - Early regulator - registry holder - MAA interaction may help bridge the gap
- EU regulatory network is developing tools to support use of disease registries
- Qualification process through EMA scientific advice may provide confidence in registry data
- Activities on registries will be prioritised in the context of EMA relocation business continuity planning

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Thank you for your attention

Further information

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