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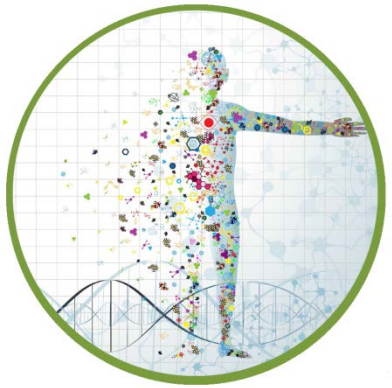
SCIENCE MEDICINES HEALTH

Use of disease registries for benefit-risk evaluation of medicines:

A regulatory perspective

DIA Europe 2018 - 17-19 April – Basel, Switzerland



DIA EUROPE 2018

Presented by Xavier Kurz
Head of Service
Surveillance and Epidemiology

Disclaimer

In this presentation:

- Why are we discussing registries?
- What is the EMA Registry Initiative?
- What are core concepts?
- What are the lessons learned from the EMA Registry workshops?
- How can regulators can support use of disease registries?
- Conclusions

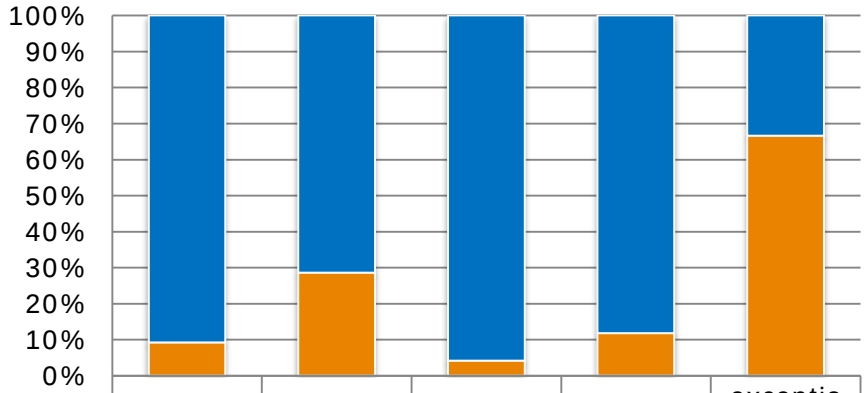
Why are we discussing registries?

Use of registries is often requested by regulators to companies in the context of risk management plans and other regulatory requirements, e.g. for advanced therapies, medicinal products for paediatric use and orphan products.

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

Overall, use of a registry imposed for 9% of the 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

Why are we discussing registries?

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Problems observed with requested registry studies

Analysis based on evaluation of European Public Assessment Reports, study protocols, Periodic Safety Update Reports, and PSUR assessment reports – data lock: 30 June 2015

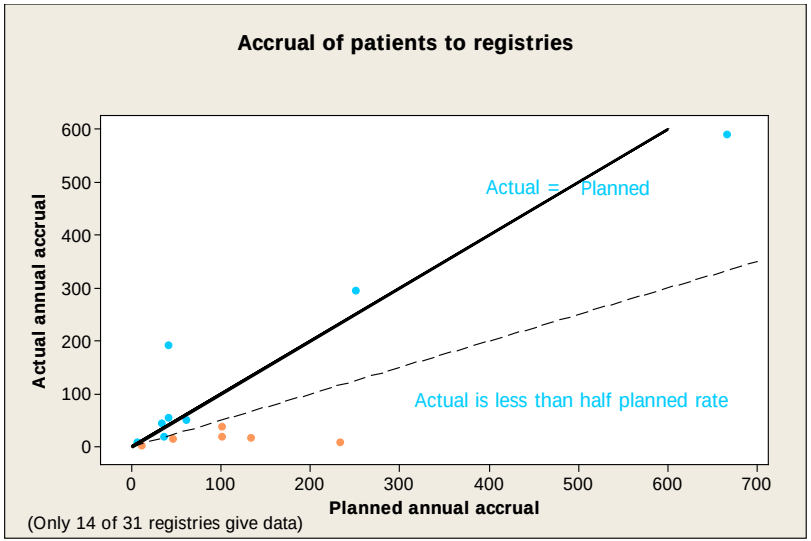
Problem	N	%
No problems reported	9	37.5
Delayed start	9	37.5
Low accrual rate	13	54.2
Protocol amendment required	9	37.5
Low data quality or missing data	3	12.5
Low use of product	3	12.5
Enrolment reduced due to other issues	3	12.5

Percentages are based on a total of 24 registries that initiated patient inclusion.

65% of registries are product specific
80% of registries are new registries

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

Actual vs. planner number of patients included



● < 50% inclusion

Why are we discussing registries?

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The approach to registries is often suboptimal in scientific and resource terms:

- Existing disease registries are not fully exploited, which may lead to duplication of efforts and inefficiencies
- Discrepancy between data collected by registries and data requested by regulators
- Use of registries faces challenges around:
  - 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)
- For these reasons, companies may prefer to establish individual product registries rather than utilise existing disease registries.

What is the EMA's Patient Registry Initiative?

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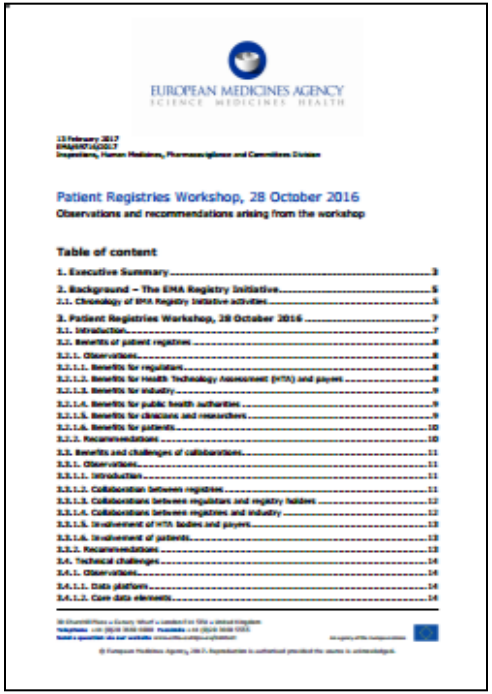
- Launched, September 2015 - set-up of a Cross-Committee Task Force
- **Aims to facilitate use of disease registries by introducing and supporting a systematic approach to their contribution to the benefit-risk evaluation of medicines.**
- **Pilot phase, 2016**: Stakeholder feedback encouraged an active role of EU network in supporting collaboration for greater utilisation of disease registries
- **28th October 2016 - Patient Registries workshop**
- **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

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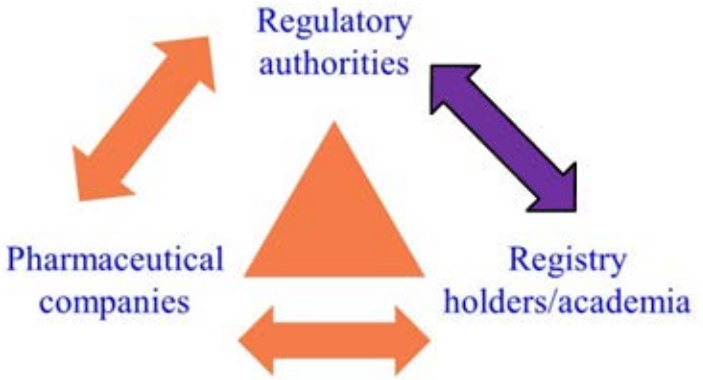
What is the EMA's Patient Registry Initiative?

Key components of the strategy

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



- To clarify the concepts: **registry vs. study**

Source: Nicola Ruperto, PRINTO

What are the core concepts?

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***Registry**:*

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 *disease registries* to *product registries* as they gather insights on clinical outcomes of conditions with different treatments, rather than on the outcomes of specific treatments, and they allow comparisons. Disease registries are also generally better integrated into health care systems.

***Study**:*

Detailed investigation and analysis of a research question or hypothesis in a population.

Post-authorisation safety (PASS) and efficacy studies (PAES) may be imposed as legal obligation.

What are the core concepts?

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	Registry	Registry-based study
Nature	Data repository	Non-interventional study, secondary data collection
Timelines	Open-ended, long-term	Defined by study objective
Cohort definition	Exhaustive within the boundaries of the selection criteria (e.g. all patients treated for cystic fibrosis in the country)	Defined by research objective with consideration to selection biases and confounding
Data collection	Different types of data can be collected, e.g : - demographics - disease outcomes - treatments - genetic data - PRO : QoL, disability, cost units	Restricted to what is needed by research question, including data on potential confounding factors (co-morbidities, co-therapies, lifestyle factors,...)
Analysis plan	Not necessarily pre-defined	Defined in protocol
AE collection and reporting	Routinely to PhV system	Routine + defined by timelines described in the protocol

Are disease registries valid and reliable data sources to conduct PASS/PAES?

What are the core concepts?

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Disease Registries

Strengths

- Natural history of disease - disease burden
- Standard of care
- Patient stratification
- Not restricted to one product, comparative analysis is possible
- Well suited to joint collaborative studies
- Open label studies possible
- Capture off label use
- Capture information on high risk groups and rare diseases
- Patient reported outcomes
- Possibility to collect additional data (depends on funding)

Limitations

- Substantial set up and running costs (sustainability)
- Co-medications and co-morbidities frequently missing
- ADRs not routinely recorded
- Lifestyle factors (smoking, alcohol, …) often missing
- Data ownership/governance challenges
- Data quality and monitoring
- If the denominator is not clear, incidence cannot be calculated

Lessons learned from the 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, HTA bodies, patients' and HCPs' representatives

Why were these diseases chosen?

- ✓ Number of products have been authorised or are in the authorisation process
- ✓ New products in the business pipeline
- ✓ EU disease registries have requested support for harmonisation
- ✓ On-going qualification procedure for two EU-wide registry platforms

Lessons learned from the EMA registries workshops

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Common core data elements

- All participants could agree on **core data elements to be collected** in disease-specific registries as a basis for regulatory evaluations
- Difference made between “must have” and “nice to have”
- Additional data can be collected if needed to support a study – needs **early discussions**

Data quality

- **Key components** : uniformity, representativeness, consistency, completeness, accuracy, timeliness - source data verification procedure
- **Data quality control system** to be established internally, **external audit to be considered**
- **Data quality indicators** to be defined
- Data quality to be similar in routine and in registry-based studies

Governance

- Regulators and MAHs to be aware of data that can be feasibly be collected by registries and inform registries on their data needs - needs **early discussions**
- Registry holders to establish **system for centralised data application requests**
- Registry holders to develop **policy for data sharing** based on data protection and informed consent
- Process for **collection and reporting of AEs** to be defined and described in study protocol - process to be in place to strongly encourage physicians to report suspected ADRs to national PhV system

How can regulators support use of disease registries?

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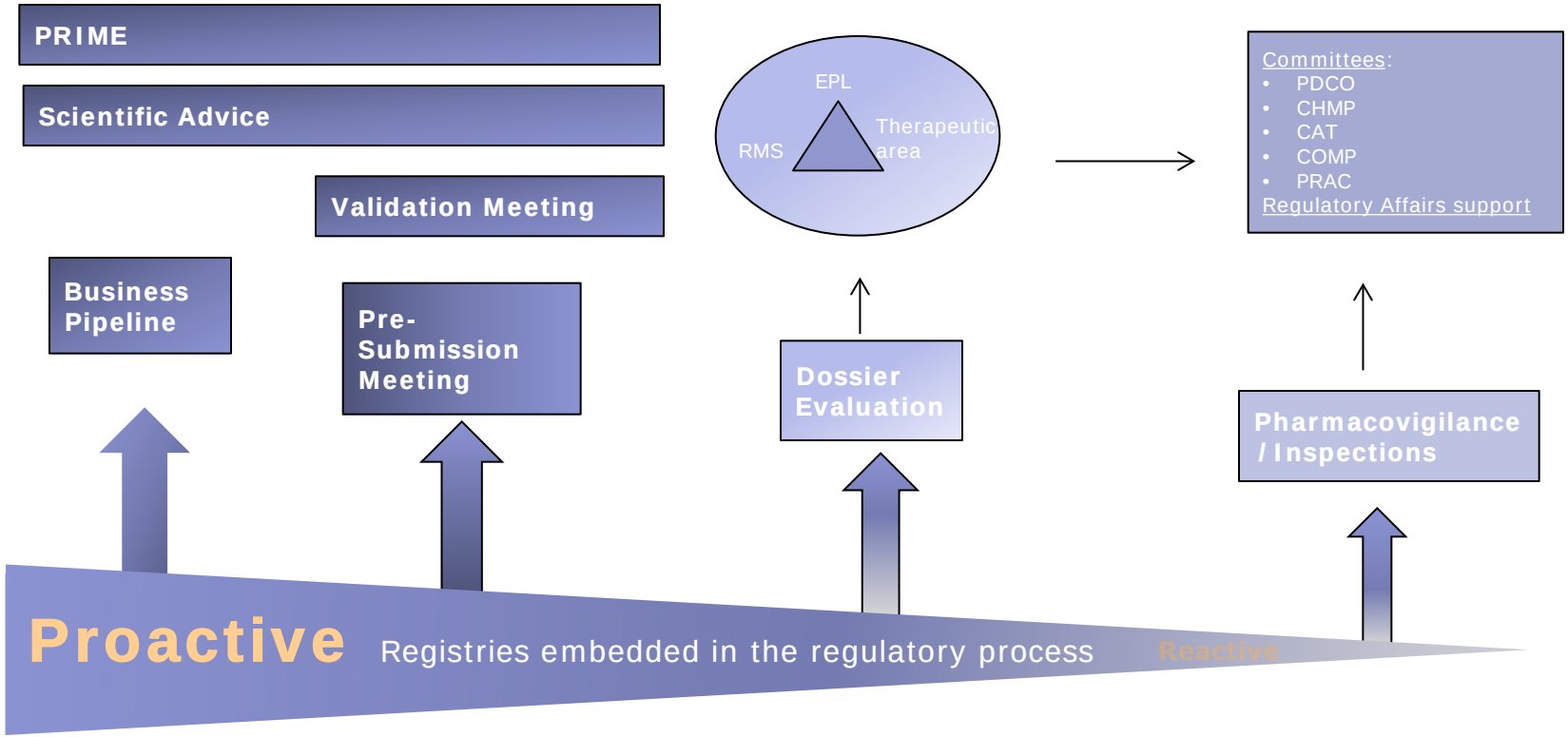
* To discuss registries at an early stage in the regulatory process



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; EPL: evaluation product lead; RMS: risk management specialist

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)

Published for consultation on EMA website

How can regulators support use of disease registries?

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* Qualification procedure

On the basis of the initial briefing document and additional information submitted during the procedure, CHMP considers that the current status of the ECFSPR (coverage, core dataset, governance, quality assurance approaches, and completeness of core variables), may allow its use as a data source for regulatory purposes in the context of the following studies concerning medicines authorised for the treatment of cystic fibrosis:

- Drug utilisation studies for total recorded population and by subgroup such as CF complications, age, gender, FEV1 status, genotype, etc.
- Drug efficacy/effectiveness studies
  Data from the ECFSPR could be used:
  - For concurrent assessment of post authorisation efficacy/effectiveness using annual best FEV1, mortality, pulmonary exacerbations using the ECFSPR working definition, or CF complications;
  - As a source of historical control data that could be used for contextualization, e.g. for comparative purposes in the context of non-randomized clinical trials (i.e. when this would be the only reasonable option).
- Drug safety evaluation
  The ECFSPR could be used as a tool to collect safety data with a particular focus on important identified and potential risks. In this context, not only assessment of cumulative annual incidence of potential or identified risks (adverse events) (i.e. currently recorded as CF complications or mortality) may be possible but also comparative assessment of new solicited safety data (adverse events of special interest) provided an appropriate control cohort can be constructed, i.e. if patients not exposed to the drug of interest are also monitored for the AE of interest.

How can regulators support use of disease registries?

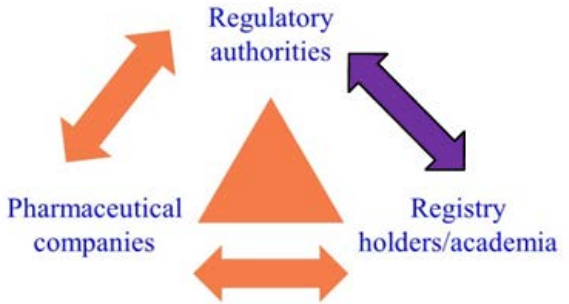
* **Methodological guidance** on use of disease registries from a regulatory perspective : forthcoming

  Will address a.o. regulatory requirements and guidance for collection and reporting of AEs and ADRs

* **Scientific Advice** on PASS/PAES study protocol using registries, e.g. joint collaborative studies

* **Inventory of disease registries** in ENCePP Resource database [www.encepp.eu]

- **Facilitation of interactions** between regulators, industry and registry holders at an early stage of product development and during the entire life cycle of the product.



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 revealed high interest from companies and registry holders to collaborate
- ✓ Gap between the amount/type of data collected in disease registries and data requested by regulators
  - ✓ Early interactions between regulators and registry holders may help bridge the gap
- ✓ EU regulatory network develops tools to support use of disease registries
- ✓ Qualification process through EMA scientific advice may provide confidence in registry data

For further information, see EMA webpage on Patient Registries

 http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000658.jsp

Thank you for your attention

Further information

Contact us at EMAregistries@ema.europa.eu

European Medicines Agency
30 Churchill Place • Canary Wharf • London E14 5EU • United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
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