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Post-licensing evidence in medicines regulation

EMA – Payer Community meeting

18 June 2019

Presented by: Xavier Kurz

Real-world evidence in medicines regulation

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Disease epidemiology

- Unmet medical needs
- Natural course of the disease following standard of care
- Disease incidence/prevalence
- Differences in clinical practice
- Comparison of surrogate and clinical outcomes
- Development/validation of clinical predictor model for treatment response
- Measurement of background rate of events (for assessment of drug safety)
- Characterisation /representativeness of patients in disease registry

Product-related investigations

- Drug utilisation – use in different age groups (children) –off label use
- Relevance of clinical trial data vs. clinical practice
- Safety monitoring and evaluation
- Planning and conduct of PASS/PAES
- (Comparative) effectiveness
- Extrapolation of adult data to children
- Pragmatic clinical trials

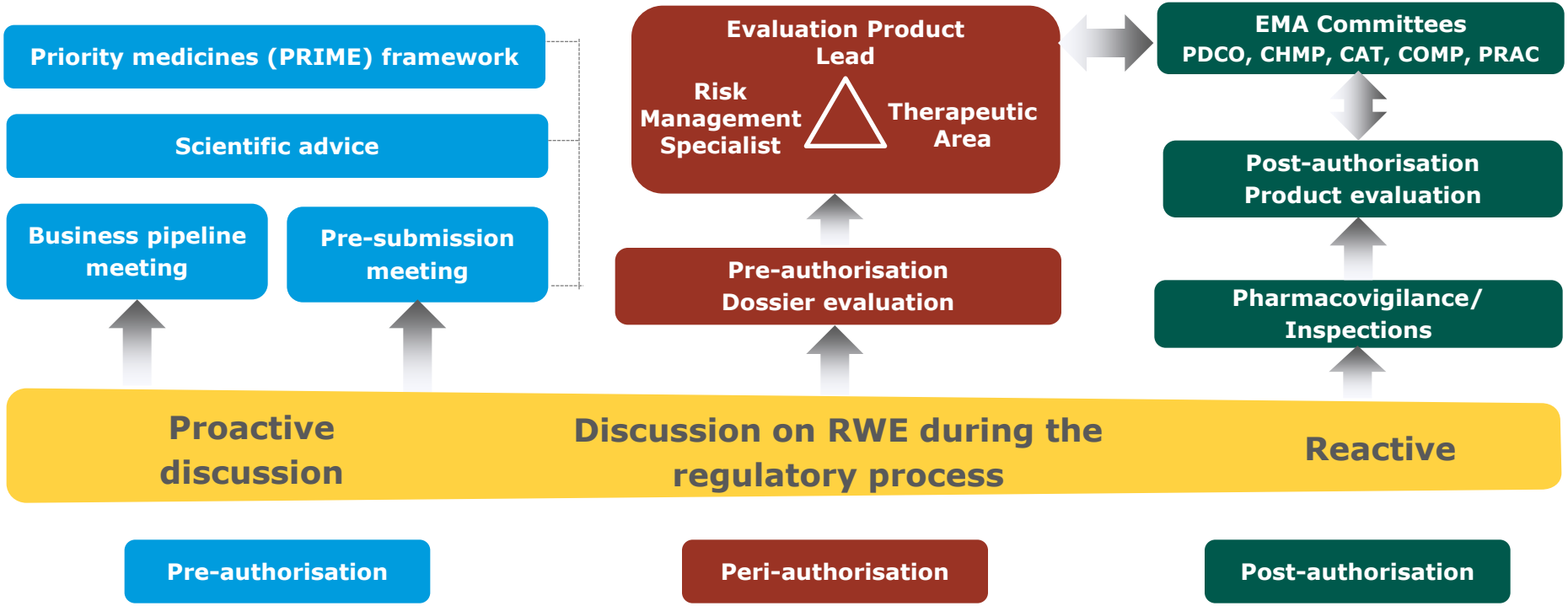

Figure 1 – Opportunities for RWE consideration during the authorisation process

RWE: Real-world evidence; CAT: Committee for Advanced Therapies; CHMP: Committee for Medical Products for Human Use; COMP: Committee for Orphan Medicinal Products; PDCO: Paediatric Committee; PRAC: Pharmacovigilance Risk Assessment Committee.

Which datasources for real-world evidence?

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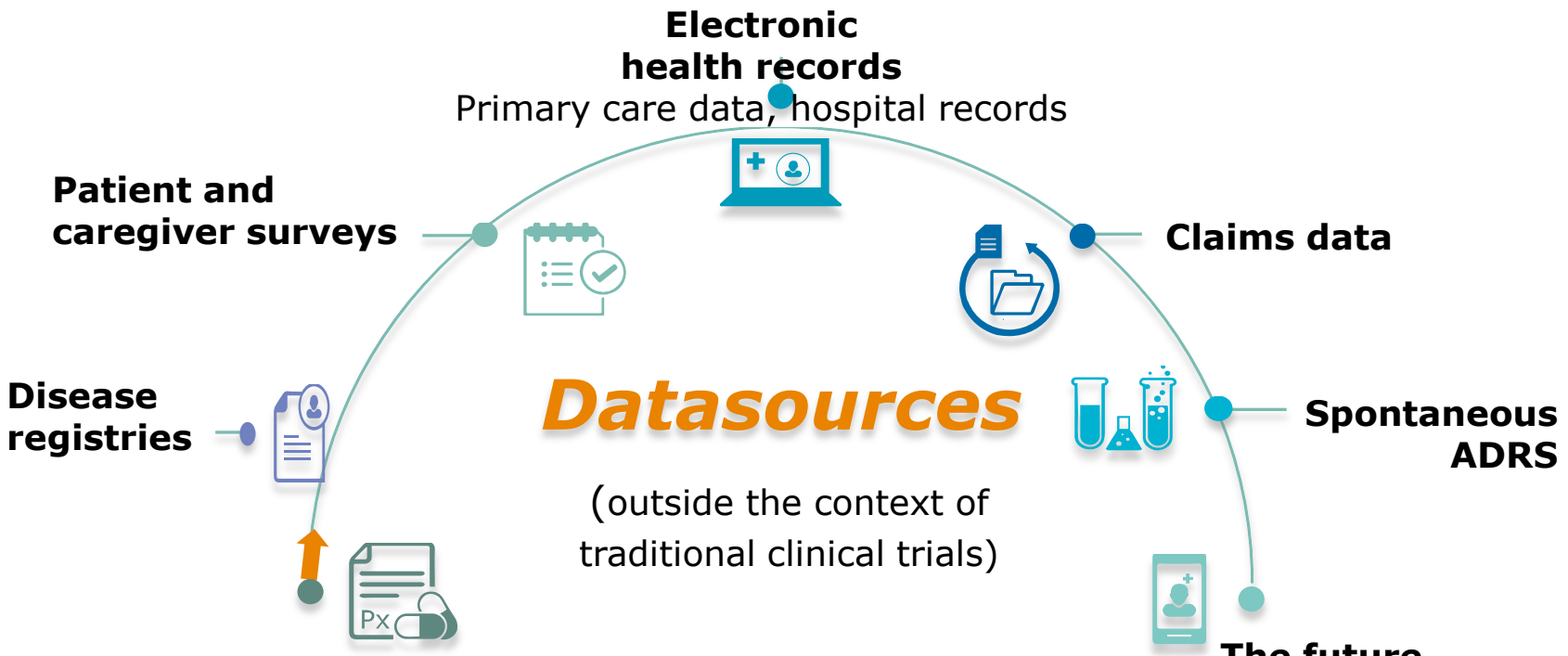

Regulatory challenges in use of RWE

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	Examples
Operational	Timely data access to data sources across national borders, quality assurance processes, transparency of reporting, development of sustainable infrastructures, data privacy and ethical considerations
Technological	Coding systems, terminologies, data formats, quality, data linkage, scope and content
Methodological	Management of biases, confounding, missing data, interpretation of heterogeneous results, feasibility analysis, validation of data sources and new methodological approaches eg common data model

OPTIMAL framework

Challenges with use of electronic health databases

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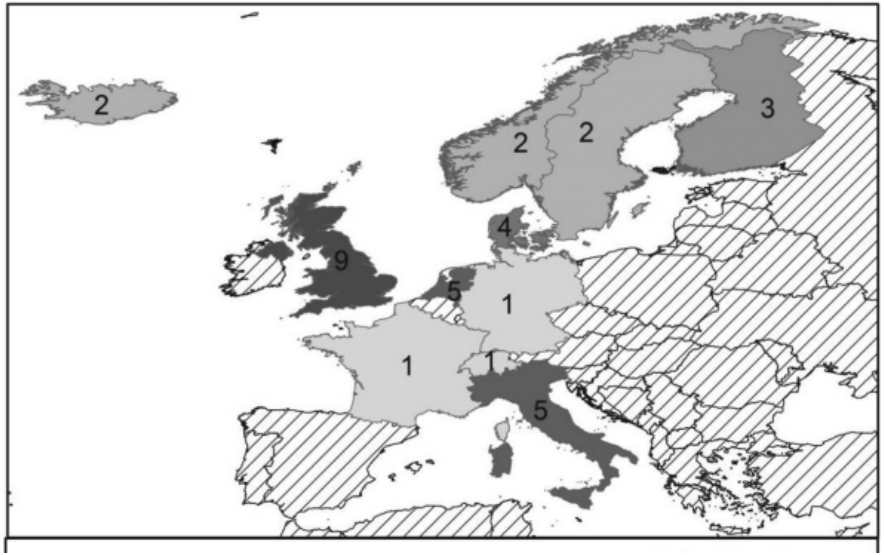
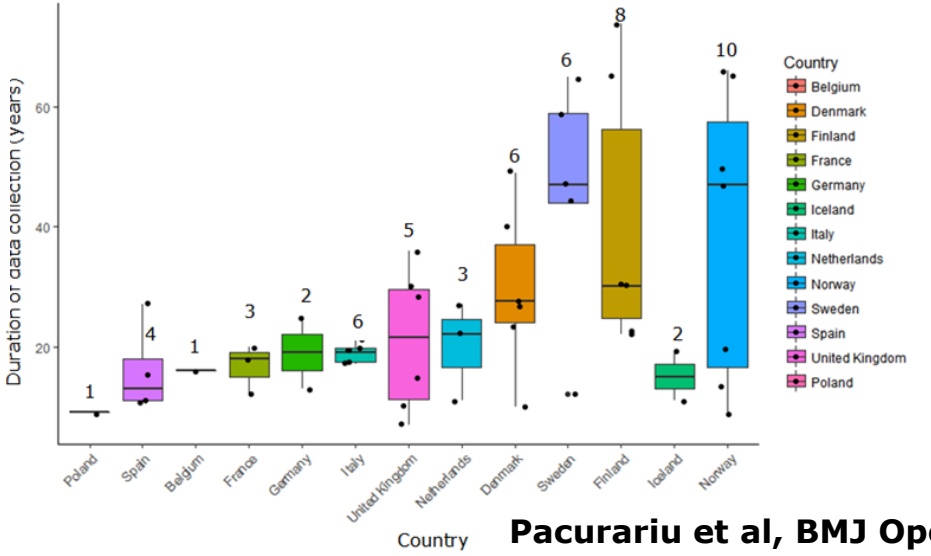
Limited representativeness across Europe



Only 13 member states have electronic health databases suitable for regulatory decision making



Limited number of European countries contributing to multi-database studies

Pacurariu et al, BMJ Open

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Many EHDs based on general practice

Percentage of substances discussed in three PRAC meetings with adequate representation in EMA in-house databases (THIN UK, IMS-France, IMS-Germany)

Table 3. Percentages of substances with adequate frequency in EMA in-house databases

	NAPs	CAPs	All
n	*29*	*70*	*99*
In at least one database	82.8	44.4	53.5
In at least two databases	75.9	27.1	41.4
In the three databases	58.6	21.4	32.3

NAP: nationally-authorised products

CAP: centrally-authorised products

Use of disease registries - example

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Zalmoxis - Adjunctive treatment in haploidentical haematopoietic stem cell transplantation (HSCT) of adult patients with high-risk haematological malignancies.

Pivotal trial – single arm Phase I/II study with an endpoint of immune reconstitution defined as CD3+ cells>100/μL + a Phase III trial.

A comparison of the treated patients (from both studies) with suitable historical controls was requested.

The EBMT patient registry was used to compile an appropriate control group selected on same criteria as the control arm of the on-going Phase III trial and a specific set of matching parameters.

Use of disease registries - example

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Eculizumab (Solaris) Paroxysomal nocturnal haemoglobinuria (PNH) in a restricted patient population with a prior history of transfusions

- MAH wished to extend the indication to patients without a prior history of infusions.
- A global PNH registry across all stages of disease was utilised to provide data to support the extension of the indication

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

Haemophilia Registries
Workshop: 8th June 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

Challenges with disease registries

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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

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5 November 2018
EMA/763513/2018

Discussion paper:

Use of patient disease registries for regulatory purposes – methodological and operational considerations

The Cross-Committee Task Force on Patient Registries

Qualification opinions

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

Qualification Opinion

The European Cystic Fibrosis Society Patient Registry (ECFSPR)

29 June 2018
EMA/CHMP/SAWP/423488/2018
Committee for Medicinal Products for Human Use (CHMP)

Draft qualification opinion on Cellular therapy module of the European Society for Blood & Marrow Transplantation (EBMT) Registry

"The current status of ECFSPR (coverage, core dataset, governance, quality assurance approaches and completeness of core variables) may allow its use for:

- **Drug utilisation studies** for total recorded population and subgroups
- **Drug efficacy/effectiveness studies**
  - Concurrent assessment of effectiveness, in specific circumstances
  - Source of historical control data for comparative purposes in the context of RCTs (i.e. when this would be the only reasonable option)
- **Drug safety evaluation**
  - Safety data with focus on important identified and potential risk: incidence, comparative risk assessment studies "

Conclusions

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- Rapidly changing scientific landscape is challenging the traditional drug development paradigm increasing the data needs
- Increasing availability of data offers the possibility of capturing a more holistic picture of the patient and provide novel insights but multiple challenges in understanding the reproducibility and validity of the derived evidence.
- It is critical to "know your data" in order to be able to decide if it is fit for purpose.
- Limited availability / accessibility to good quality RWD – most electronic health record databases are based on GP practices
- Disease registries may offer data on medicines used in secondary/tertiary care but data quality and adequacy need to be addressed

Thank you for your attention