EU Framework for RWE

Real World Evidence and Regulatory Decision Making

Joint CSPS and Health Canada Workshop

Presented by Dr Peter Arlett 3 December 2019
Head of Pharmacovigilance and Epidemiology, EMA
In this talk

EU Framework for RWE

• A bit about Europe
• Challenges and opportunities
• RWE through the product lifecycle
• Experience @EMA
• Making it better
• Watch out for more
Key messages

• EMA strives to meet the needs of patients for new and better treatments
• Already today RWD forms an important part of the evidence used to regulate drugs
• Evidentiary value depends on:
  • the regulatory use case (safety, efficacy, effectiveness)
  • The product and disease
  • The data (quality, representativeness)
• Need for: data access; data quality framework; data governance; analytics technology; new processes; training.
• Approach: multi-stakeholder and international – deliver through collaboration
• Watch out for recommendations of the Big Data Task Force and EMA Regulatory Science Strategy
Real-World Data (RWD): routinely collected data relating to patient health status or the delivery of health care from a variety of sources other than traditional clinical trials.

Real-world evidence (RWE): information derived from analysis of real-world data.
The European Union landscape

- Over 500 million people living in the European Union
- 28 member states
- 27% of global sales of medicines
- 24 official languages

EMA in the EU

Who do we work for?

Different cultures

Different religions

Different lifestyles

Different medical terminologies

... with different therapeutic guidelines

... different healthcare and reimbursement systems

But: innovative medicines are authorised centrally at EU level with same product information...
3. Landscaping of datasources and initiatives in EU

Characterisation of EHR databases in Europe

BMJ Open  Electronic healthcare databases in Europe: descriptive analysis of characteristics and potential for use in medicines regulation

Alexandra Pacuraru,1 Kelly Plueschke,1 Patricia McGettigan,1,2 Daniel R Morales,1,3 Jim Slattery,1 Dagmar Vogl,1 Thomas Goedecke,1 Xavier Kurz,1 Alison Cave3

30%-50% of all PASS use EHDs as their main data source

Use of EHDs in pre-authorisation research is currently limited (understanding the natural history of diseases, historical control data)

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

High heterogeneity in data collected or available through linkages and in data quality
Inventory of patient registries in ENCePP Resource database

Currently: 86 disease/case registries
New Regulatory Challenges

• Increasingly complex trial designs with modelling and simulation approaches
• Increasing biomarker use
• Increasing disease stratification/personalised medicine
• Increasing numbers of products unable to align with traditional drug development pathway
• Wearable devices – smart apps – mobile health

Measure of effectiveness in clinical practice based on composite endpoints and patient reported outcome measures
• More combination therapies and challenge for safety
• Personalisation of dose and risk profiles
• Incorporation of patient preferences into decisions
• New “big” data sources

Pre-authorisation

Authorisation

Post authorisation
Need for real world evidence in the product life-cycle

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
Classified as public by the European Medicines Agency

2013-2019: 88 EMA in-house RWE studies to support Scientific Committees
- 50 using THIN (UK EHRs)
- 34 using IMS FR/DE
- 22 using EudraVigilance
- 8 systematic review/meta-analysis
- 2 with other regulatory agencies

Association between systemic fluoroquinolone exposure and tendon rupture: population-based nested case-control study

Association between hydrochlorothiazide exposure and skin cancer: a series of population-based case-control studies

Cohort Study of Psychiatric Adverse Events Following Exposure to Levonorgestrel-Containing Intrauterine Devices in UK General Practice
## EMA-funded studies

19 external RWD studies to support EMA Committees (2010-2019)

### EMA-funded studies

<table>
<thead>
<tr>
<th>Study</th>
<th>N databases</th>
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<tbody>
<tr>
<td>A/H1N1 pandemic vaccines and pregnancy outcomes</td>
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<td>Impact of risk minimisation in patients treated with rosiglitazone-containing products</td>
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<td>Isotretinoin and the effectiveness of the Pregnancy Prevention Programme in Europe</td>
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<td>Patterns and determinants of use of oral contraceptives in the EU</td>
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<td>Monitoring the effectiveness of risk minimisation in patients treated with pioglitazone-containing products</td>
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<td>Risk of cardiac valve disorders associated with the use of biphosphonates</td>
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<td>Association between anxiolytic or hypnotic drugs and total mortality</td>
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<td>Metformin use in renal impairment</td>
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<tr>
<td>Study of regulatory communication and risk awareness following the Article 31 referral of Combined Hormonal Contraceptives in relation to thromboembolism</td>
<td>n/a</td>
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<tr>
<td>Characterising the risk of major bleeding in patients with Non-Valvular Atrial Fibrillation: non-interventional study of patients taking Direct Oral Anticoagulants in the EU</td>
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<td>Study of utilisation of Combined Hormonal Contraceptives in Europe</td>
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<td>Anti-microbial resistance: choice of therapeutic interventions and outcomes for the treatment of infections caused by MDR Gram negative pathogens</td>
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<td>Methods and data sources for determining long-term effects of drug exposure during pregnancy, with application to antiepileptic medicines</td>
<td>n/a</td>
<td>28</td>
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<td>Impact of EU label changes for systemic diclofenac products: post-referral prescribing trends</td>
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<td>3</td>
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<tr>
<td>Impact of EU label changes for hydroxyzine products: post-referral prescribing trends</td>
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2019: 5 studies committed:
- 2 valproate
- 2 retinoids
- Ranitidine
Collaborations with FDA and Health Canada

- Study: Characterising the risk of major bleeding in patients with Non-Valvular Atrial Fibrillation: non-interventional study of patients taking Direct Oral Anticoagulants in the EU.
  - EMA-funded and HC-funded study performed in parallel in the EU and in all Canadian Provinces (except Quebec) based on EU-led common protocol.
  - Study performed in parallel by FDA in Medicare database
  - Results and methodologies discussed (together with PRAC Rapporteur)
  - CHMP Assessment of results triggered by EMA ED under Art 5(3)

  Opportunity to use larger populations and different comparator groups and to exchange on different approaches.

- Setting-up of exchange mechanisms on approaches for better use of RWE decided at EMA/EC-FDA bilateral meeting, Brussels, June 2018 – quarterly teleconferences
Making it better
Developing an **OPTIMAL** framework for regulatory use of RWE

Operational

Technical

Methodological

Cave A, Kurz X, Arlett P.

Interoperability and Harmonisation
- Common data models
- Minimal Data sets
- Standards
- Transparency

Characterisation
Documenting the strengths and limitations of RWD, enabling consistent validation

Making it better

Good governance
- Addressing data sharing, accessibility and privacy

Good methodology
- Study design making best use of RWD to enhance the quality of evidence
Supporting data sharing, accessibility and privacy

Evidence generation from healthcare databases: recommendations for managing change

Good Practices for Real-World Data Studies of Treatment and/or Comparative Effectiveness: Recommendations from the Joint ISPOR-ISPE Special Task Force on Real-World Evidence in Health Care Decision Making
Supporting data sharing, accessibility and privacy

Coordination of the European Network of Centres in Pharmacoepidemiology and Pharmacovigilance (ENCePP)

Centres (>150)
- Public (university, hospital, government, charities)
- Others (CROs, consultants)

Networks (>20)
- International
- National

Data sources (>120)

Transparency
- Registration of studies
- Publication of protocols and results

Independence
- Roles and responsibilities of all parties

Standards
- Methodological Guide on Research Standards
- Code of conduct

EU PAS Register
4. Learning about value and applicability of methodologies

Learning about use and validity of common data models

- Potentially, conversion of databases in CDM will allow much faster access to and analysis of data from multiple databases

- Questions remain:
  - How efficient is the conversion process (loss of information)?
  - How valid and reliable are the results generated?
  - Impact on resources?
Interoperability and harmonisation

Private-partnership with EU finding

**Federation:** Creation of an EU-wide architecture for analyses of RWD

**Harmonisation:** of more than 100 million anonymised health records to the OMOP Common Data Model

Infrastructure, tools and methods for benefit-risk monitoring of vaccines in Europe.

Network of research organisations and public health authorities

Currently: 10 data sources with partial common data model.
https://doi.org/10.1007/s40264-019-00848-9

ORIGINAL RESEARCH ARTICLE

Patient Registries: An Underused Resource for Medicines Evaluation

Operational proposals for increasing the use of patient registries in regulatory assessments

Patricia McGettigan¹, Carla Alonso Olmo², Kelly Plueschke², Mireia Castillon², Daniel Nogueras Zondag², Priya Bahri², Xavier Kurz², Peter G. M. Mol³,⁴
Supporting data sharing, accessibility and privacy

The EU General Data Protection Regulation (GDPR) is the most important change in data privacy regulation in 20 years.

The regulation will fundamentally reshape the way in which data is handled across every sector, from healthcare to banking and beyond.
Phase I December 2018:

- Characterisation of data sources
- Synopsis of the survey of NCAs and industry
- Set of core recommendations
- Annexes including reports from 7 subgroups

Phase II December 2019

- Regulatory prioritisation and implementation of recommendations
- For publication January 2020
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