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Lessons learned from the applications submitted to EMA for marketing authorisation and extension of indication, 2018- 2019

Learnings initiative webinar for optimal use of big data for regulatory purpose

Plenary session 1: Lessons learned from the submission of big data for regulatory purpose

Presented by Elisabeth Bakker on 30 November 2021
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Disclaimer

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- I have no conflict of interest to disclose

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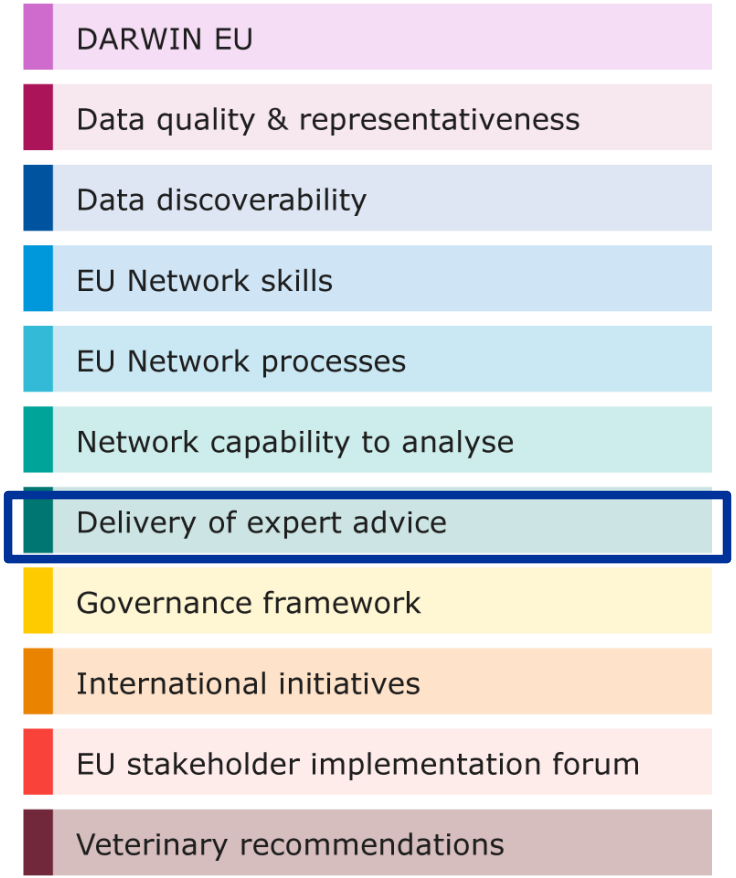
RWE in Regulatory decision making

- One of the core recommendations of the EMA Regulatory Science Strategy to 2025: "Promote use of high-quality real-world data (RWD) in decision making"
- Real-World Evidence (RWE) may support valid regulatory decisions on benefits and risks of medicinal products proposed for authorisation:
  - When RCTs are not feasible or unethical (e.g., in very rare diseases, in 'precision medicines')
  - As complementary evidence across the drug life-cycle
  - By guiding clinical trial decisions/designs (population, contextualisation etc.)

EMA Regulatory Science to 2025 (europa.eu)

Big data | European Medicines Agency (europa.eu)



Marketing Authorization Applications Made to the European Medicines Agency in 2018–2019: What was the Contribution of Real-World Evidence?

Robert Flynn[1,2,†], Kelly Plueschke[1,†], Chantal Quinten[1], Valerie Strassmann[3], Ruben G. Duijnhoven[1,4], Maria Gordillo-Marañon[1,5], Marcia Rueckbeil[1,6], Catherine Cohet[1] and Xavier Kurz[1,*]

Information derived from routinely collected real-world data has for a long time been used to support regulatory decision making on the safety of drugs and has more recently been used to support marketing authorization submissions to regulators. There is a lack of detailed information on the use and types of this real-world evidence (RWE) as submitted to regulators. We used resources held by the European Medicines Agency (EMA) to describe the characteristics of RWE included in new marketing authorization applications (MAAs) and extensions of indication (EOIs) for already authorized products submitted to the EMA in 2018 and 2019. For MAAs, 63 of 158 products (39.9%) contained RWE with a total of 117 studies. For 31.7% of these products, the RWE submitted was derived from data collected before the planned authorization. The most common data sources were registries (60.3%) followed by hospital data (31.7%). RWE was mainly included to support safety (87.3%) and efficacy (49.2%) with cohort studies being the most frequently used study design (88.9%). For EOIs, 28 of 153 products (18.3%) contained RWE with a total of 36 studies. For 57.1% of these products, studies were conducted prior to the EOIs. RWE sources were mainly registries (35.6%) and hospital data (27.0%). RWE was typically used to support safety (82.1%) and efficacy (53.6%). Cohort studies were the most commonly used study design (87.6%). We conclude that there is widespread use of RWE to support evaluation of MAAs and EOIs submitted to the EMA and identify areas where further research is required.

https://doi.org/10.1002/cpt.2461

Working definition of RWD/RWE

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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 an analysis of real-world data"

INCLUDED AS RWD/RWE

- Non-interventional pre- or post-authorisation studies with primary or secondary data collection
- Use of real-world data source (e.g. registry, electronic health care records, medical charts, etc.) in the context of clinical trials (e.g. external control groups)
- Analyses of patient-based observational data in the context of the MAA (e.g. natural history of disease, drug utilisation of reference)
- Information from published articles of product-related non-interventional studies (e.g. on safety or effectiveness in other indications)

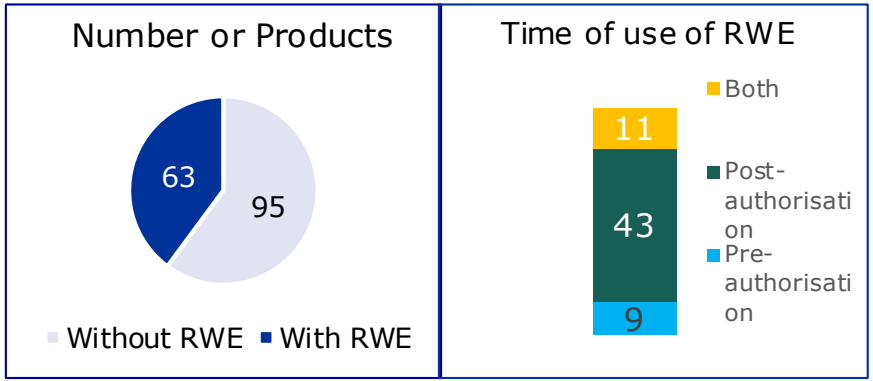
NOT INCLUDED AS RWD/RWE

- Non product-related literature review (e.g. on epidemiology of the disease)
- Interventional studies (Phase I, II), pre-clinical studies, toxicological studies, dose-response studies, drug-drug interaction studies
- Clinical trials without use of RWD/RWE
- Open-label follow-up studies of clinical trial patients
- Routine pharmacovigilance activities in RMP
- Surveys not based on individual patients (e.g. surveys of physicians to assess awareness of risk minimisation measures)

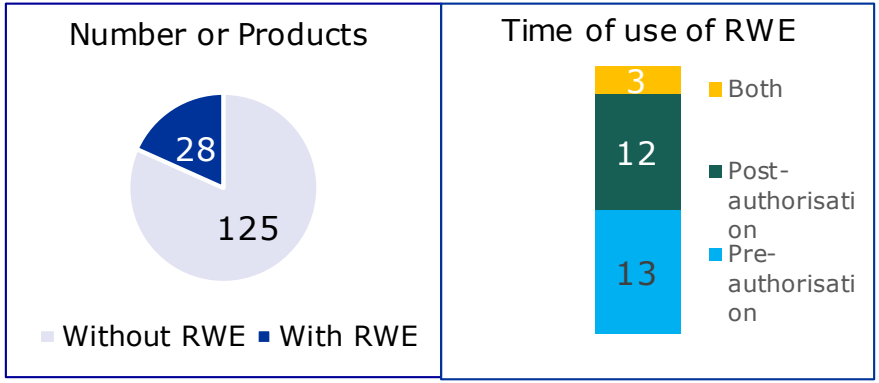
Results

- RWD/RWE used in **40% of MAAs** (mainly post-authorisation) and in **18% of EoIs** (mainly pre- or post-authorisation)
- Majority of products: **Antineoplastic** and **Immunosuppressants** (35% MAA and 42% EoI)
- When used pre-authorisation: mainly **supporting** study looking at **efficacy/effectiveness**
- When used post-authorisation: mainly **RMP Category 3** (for studies included in RMP) looking at **safety**

Initial MAA (n=158)



Extension of indication (n=153)

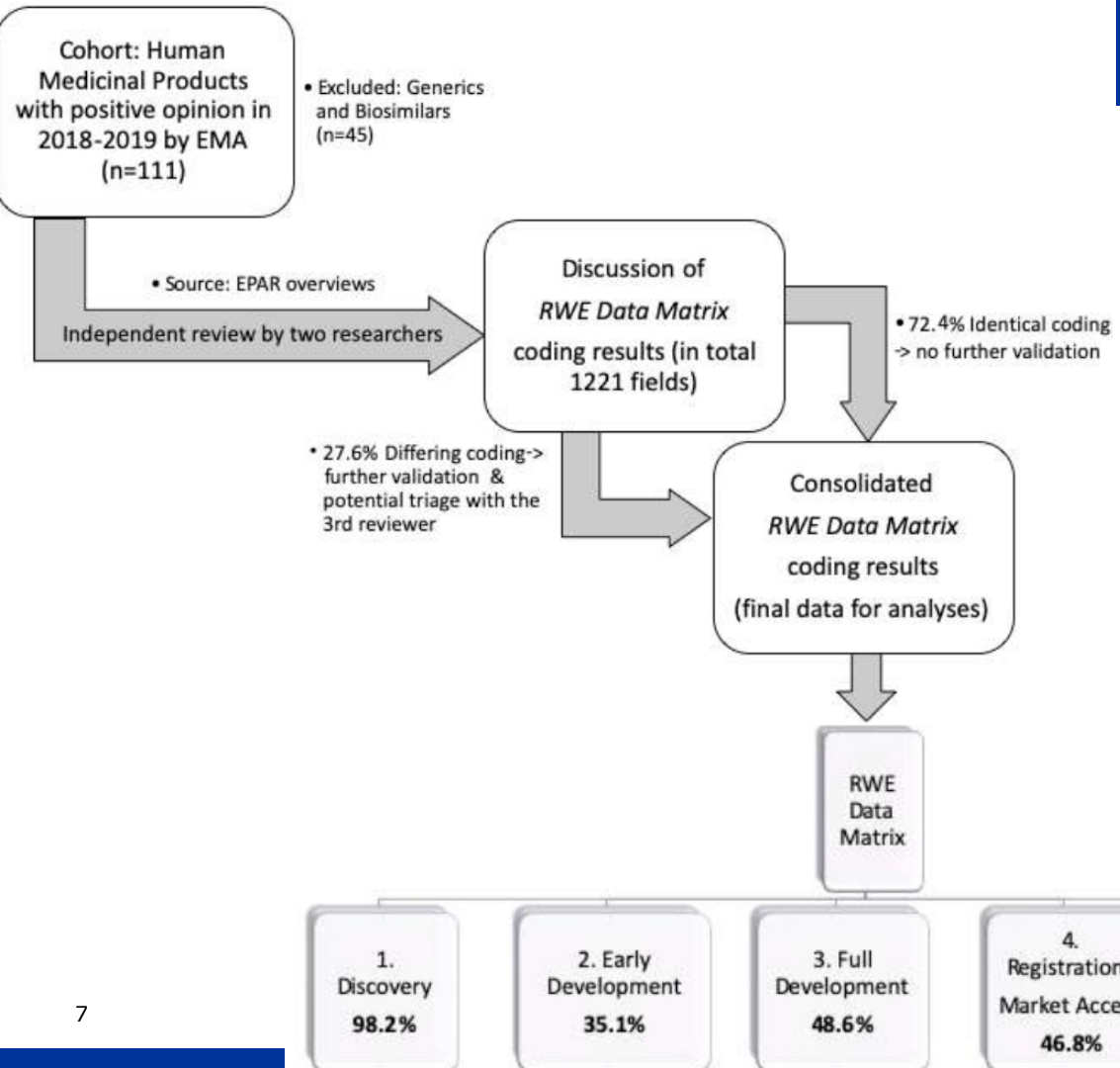


Eskola et al. (2021) Use of Real-World Data and Evidence in Drug Development of Medicinal Products Centrally Authorized in Europe in 2018–2019.

- **Aim**: to identify and quantify "the signatures of RWE use," in medicines development and regulatory decision making for the initial marketing authorization applications of new medicines evaluated with a positive opinion received in 2018 and 2019 by the EMA
- **RWE signature**: "***any reference*** to potential use of RWD/RWE in the marketing authorization application as presented in the EPAR overview"

Eskola, S.M., Leufkens, H.G.M., Bate, A., De Bruin, M.L. and Gardarsdottir, H. (2021), Use of Real-World Data and Evidence in Drug Development of Medicinal Products Centrally Authorized in Europe in 2018–2019. Clin Pharmacol Ther. https://doi.org/10.1002/cpt.2462

Eskola et al. (2021)



- RWE signatures:
  - 100% of life-cycle management & 98.2% discovery
  - were more often seen for orphan and conditionally approved medicines.
  - Oncology, hematology and anti-infectives therapeutic areas with most RWE signatures in their ***full development phase***

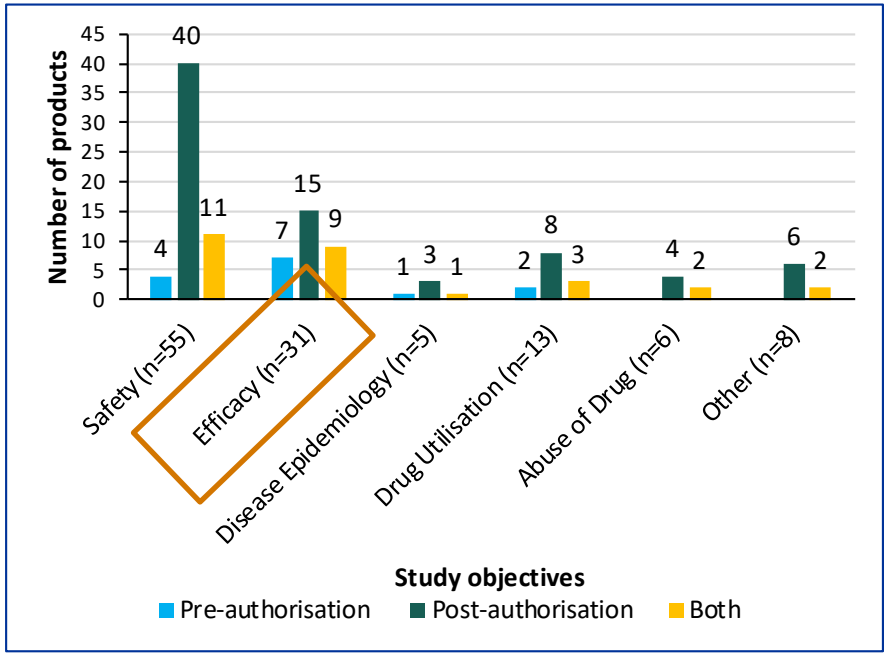
Role of RWD/RWE in applications for marketing authorisation and extension of indication submitted in 2018-2019: Phase II

Objectives:

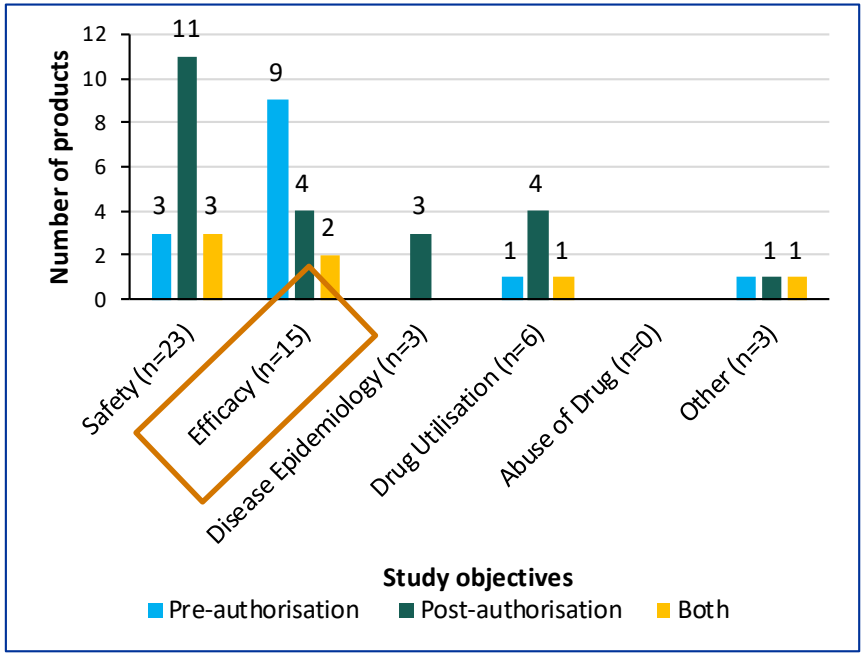
1. To characterize the RWE used by applicants **to support efficacy/effectiveness claims** on medicinal products for human use and disease epidemiology as part of marketing authorisation and extension of indications applications in 2018-2019
2. To analyse the **contribution of RWE** to the Committee for Medicinal Products for Human Use (CHMP) decision making on these marketing authorisation and extension of indications applications
3. To **provide guidance** to industry on the submission of RWE within these applications

Sample (RWE to support efficacy/effectiveness)

MAAs: RWE studies (n=138) submitted (n products=63)

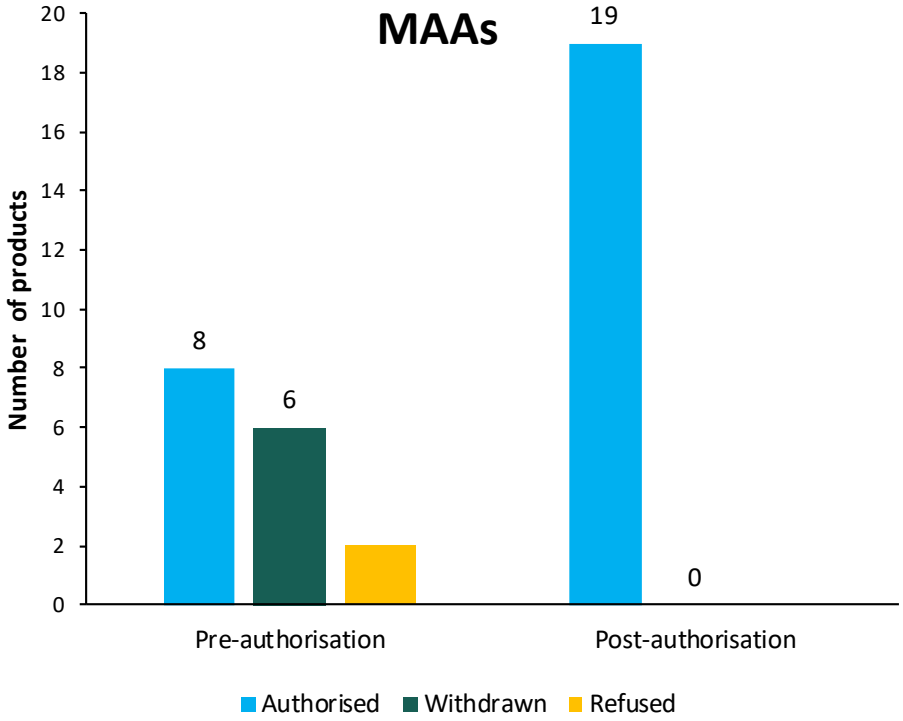


EoIs: RWE studies (n=46) submitted (n products=28)



Preliminary results

- Selected for analysis
  - **MAA: 29 products***
  - EoI: 15 products
- MAA
  - 6 products pre-authorisation RWE
  - 13 products post-authorisation RWE
  - 10 both
- Most MAAs were granted standard MA
  - 14 standard
  - 4 conditional
  - 3 exceptional



Preliminary results: Pre-authorisation RWE (16 products)

Pre-authorisation RWE (16 products)

- Main purpose of RWE:
  - Natural history, contextualization, and or external comparator
  - Primary data source

- 4 of 16 dossiers with pre-authorisation RWE critical for decision making
  - 2 examples:
    - Cufence
    - Zolgensma

Example (1): Cufence (trientine dihydrochloride) treatment of Wilson's disease in patients intolerant to D-Penicillamine therapy, in adults and children aged 5 - ≤17 years

- **Main study**: Multicentre retrospective study to assess long-term outcomes
  - **Single group cohort study** based on medical records from large tertiary care centres, 4 EU countries, 90 patients
- **Supportive study:** 12-month prospective continuation of the retrospective study, with same objectives (n=52)

- **CHMP appraisal**: Approach with observational data appropriate considering the legal basis of the application and in line with earlier protocol assistance provided

→ However, due to some limitations (sample size calculation, chosen endpoint, possible bias), a PAES was imposed by CHMP.

https://www.ema.europa.eu/en/medicines/human/EPAR/cufence

Example (2): Zolgensma (*onasemnogene abeparvovec)* a gene therapy medicine for treating spinal muscular atrophy (orphan designation)

- **Main study:** Study CL-303: Phase 3 open-label, single-arm trial (n=22)
- **External comparators:**
- Paediatric Neuromuscular Clinical Research (PNCR) Database: natural history study of 337 patients with any form of SMA followed at 3 large, tertiary medical centres
    - Natural history cohort used: all patients (n=23) with age of onset ≤ 6 months, biallelic deletion of SMN1 and 2 copies of SMN2 for whom enrolment data (retrospective and prospective)
- NeuroNext study: a longitudinal, multi-centre, prospective natural history study
    - Natural history cohort: SMA type 1 patients with bi-allelic deletion of SMN1 and 2 copies of SMN 2 (n=16).

https://www.ema.europa.eu/en/medicines/human/EPAR/zolgensma

Example (2): Zolgensma (*onasemnogene abeparvovec)* a gene therapy medicine for treating spinal muscular atrophy (orphan designation)

- **SAWP advice:**
- Internal comparator is preferred
- Some form of control necessary
- Historical controls considered adequate, but bias should be minimized

CHMP appraisal:

- Historical controls considered adequate
- PNCR cohort may include patients with less severe disease
  - not considered a major issue since the potential bias this creates i.e., these patients are expected to experience the event earlier, is not in favour of Zolgensma

→ Prospective long-term registry (RESTORE) post-approval condition of the market authorization

https://www.ema.europa.eu/en/medicines/human/EPAR/zolgensma

Conclusion

- Increasing use of RWD in MAAs
- We acknowledge the effort of applicants to provide as good RWD as possible in applications to address regulatory requirements
  - Challenges remain
- Work in progress to provide guidance to applicants on the use of RWE based on the experience we acquire
  - CHMP guideline on registry-based studies
  - This study should provide us with relevant information to be included in future guidance documents

Thank you for your attention!

Further information

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