Disclosures

There were no conflicts of interest within the scope of this work

1. **Putnam** Inizio Advisory

Putnam
Inizio Advisory

Use of Real-World Evidence in European Medicines Agency Decisions

Ulrike Kuchenbecker[1], Catherine Watson[2], Gabriel Jones[3], Caroline Shaw[4]

[1] Director, HTA & Market Access Strategy, Putnam PHMR, London, UK; [2] Market Access Research Scientist, Putnam PHMR, London, UK; [3] Senior Information Specialist & Systematic Reviewer, Putnam PHMR, London, UK; [4] Principal Market Access Research Scientist, Putnam PHMR, London, UK.

Background

Putnam PHMR

- Real-world evidence (RWE) and real-world data (RWD) may play an important role in complementing clinical trial data to support the clinical effectiveness of a medicinal product in regulatory submissions

- ISPOR HEOR trends[1] noted specific use of RWE in FDA drug approvals, e.g.:

Ibrance® (palbociclib), 2019: RWD from electronic health records provided additional supportive data to characterise Ibrance in combination with endocrine therapy in male patients with breast cancer

The rare nature of male breast cancer suggested multiple sources of data were needed to evaluate efficacy[2]

Erbitux® (cetuximab), 2021: RWD supported a new dosing regimen[1]

Abbreviations: FDA, Food and Drug Administration; HEOR, health economics outcomes research; RWD: real-world data; RWE: real-world evidence

Study Objectives

Primary objective

- To conduct a review to identify the prevalence with which RWE was evaluated in EMA regulatory decisions

Secondary objectives

- To investigate the potential solutions offered by RWE/RWD
- To identify the challenges highlighted by RWE/RWD

Abbreviations: EMA, European Medicines Agency; RWD, real-world data; RWE, real-world evidence

Methods (1)

- The EMA website[3] was searched to find European Public Assessment Reports (EPARs) that were published during the previous year, and which included RWE/RWD-related terminology
- The following in-built filters were applied:
  - Categories: Human
  - Medicine: EPAR
  - First published from 20/06/21 to 20/06/22
- Keywords were adapted from the free text terms used in the Observational Studies search filter developed by the Scottish Intercollegiate Guidelines Network (SIGN)[4] and supplemented by additional RWE/RWD-related terms

Abbreviations: EMA, European Medicines Agency; EPAR, European Public Assessment Reports; RWD, real-world data; RWE, real-world evidence; SIGN, Scottish Intercollegiate Guidelines Network

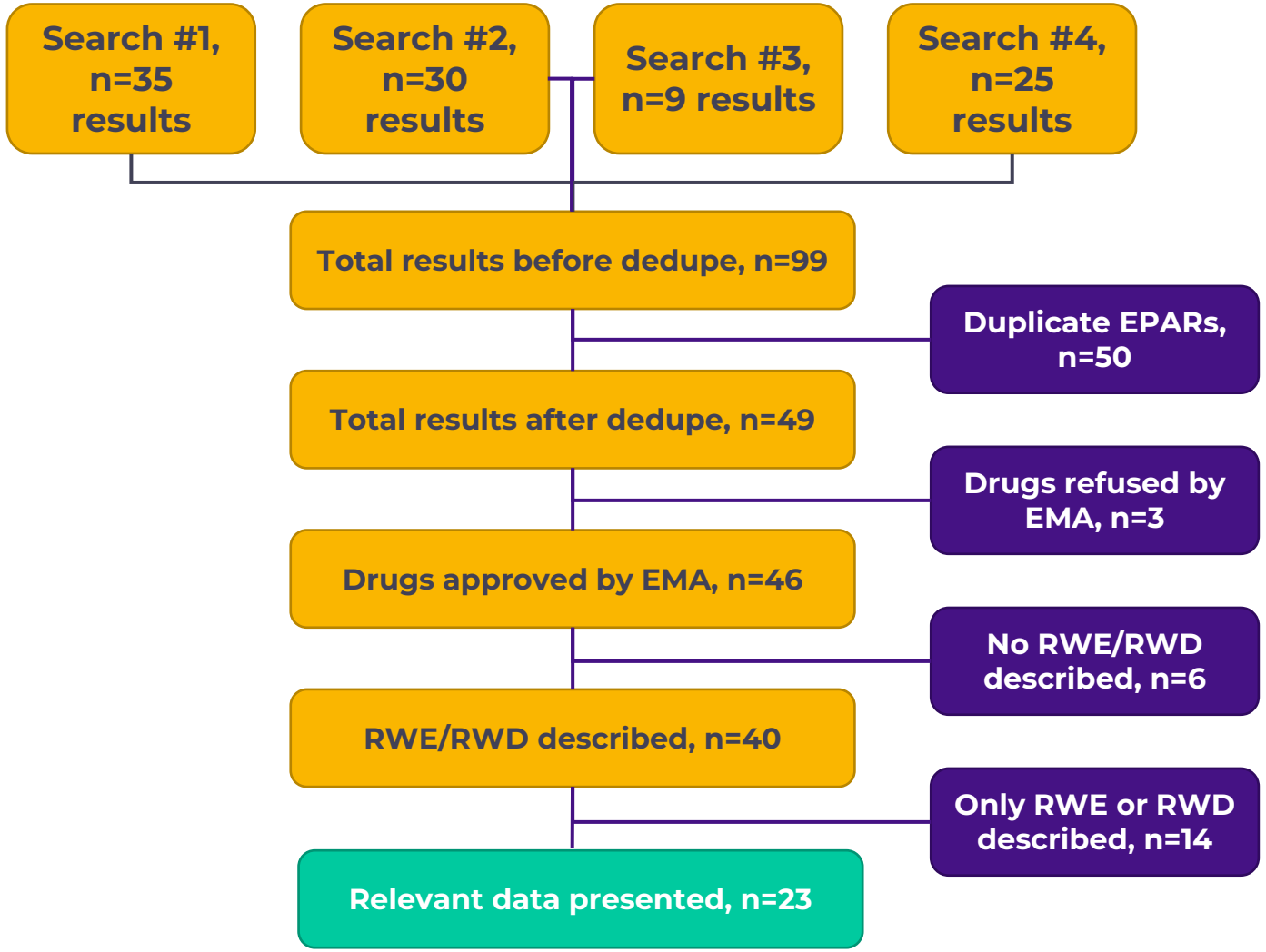
Methods (2)

- Due to a character limit on the EMA website search interface, RWE/RWD-related keywords were split into 4 separate searches
- The results of these were then compiled and deduplicated
- A data extraction template was designed in Excel to extract the following data for each drug:
  - Brand/generic name
  - Indication
  - Therapeutic area
  - Publication date
  - Context and details of RWE/RWD
  - Post-authorisation obligations

Abbreviations: EMA, European Medicines Agency; EPAR, European Public Assessment Reports; RWD, real-world data; RWE, real-world evidence

Study summary

- 76 EPARs were first published by the EMA for assessed drugs
- 49 EPARs were retrieved following deduplication
- Of these, 46 (94%) were for drugs that received EMA approval
- RWE/RWD was mentioned in the Public Information or Public Assessment Report documents of 40 (87%) approved drugs
- However, only 23 (58%) of these presented relevant data

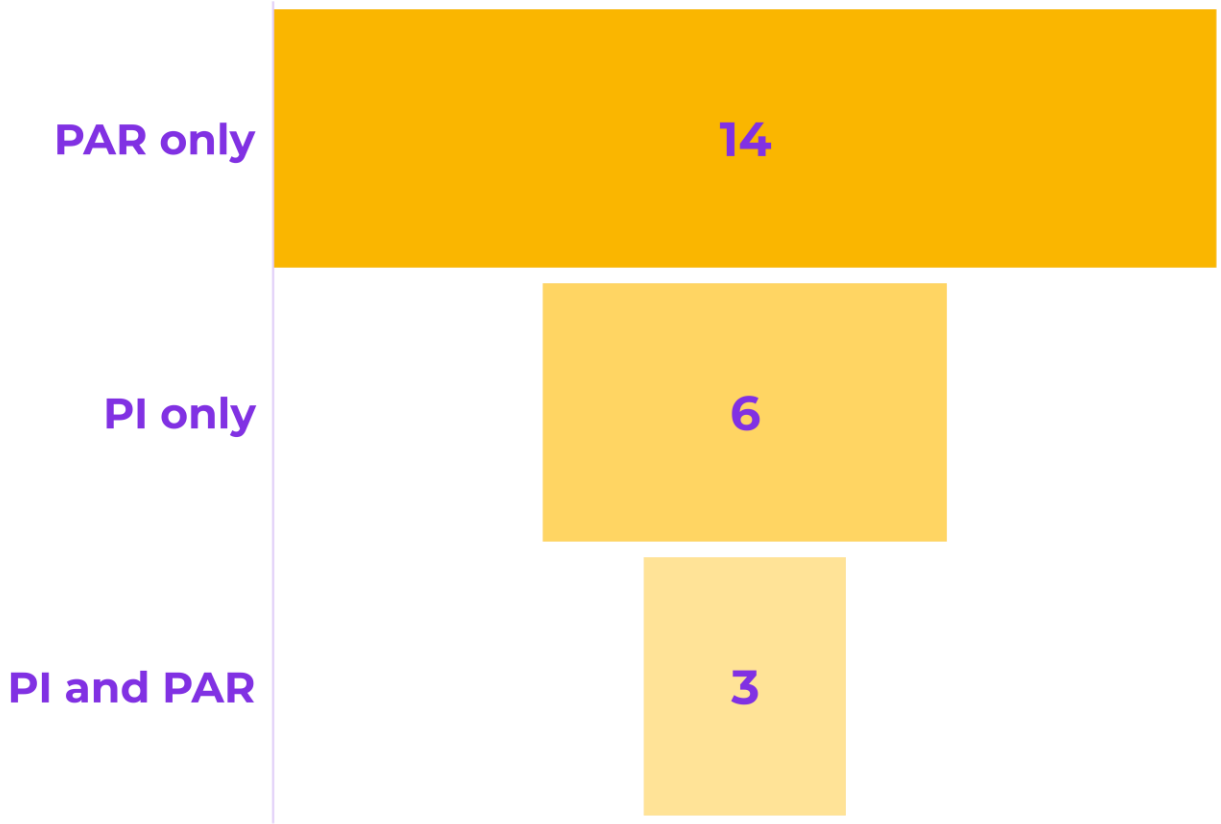


Abbreviations: EMA, European Medicines Agency; EPAR, European Public Assessment Reports; RWD, real-world data; RWE, real-world evidence

RWD reporting

- RWD were reported for 30% (n=23) of all assessed drugs, either descriptively or quantitatively
- Reported more frequently in the Product Assessment Report (PAR; n=17) than in the Product Information (PI; n=9)

Figure 1. Funnel plot representing EPARs with RWD reported in the PAR, PI, or both documents

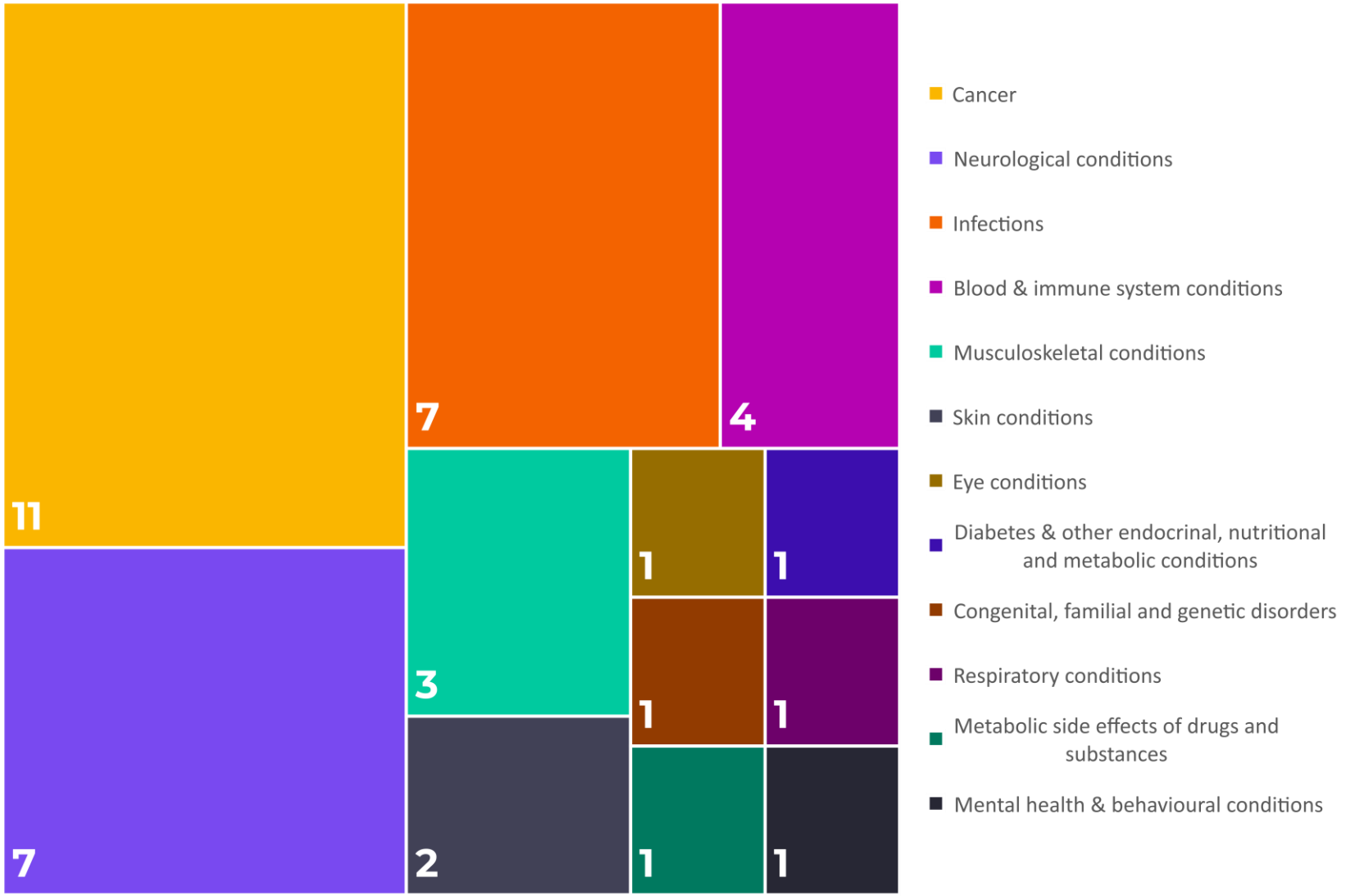


Abbreviations: PAR, Public Assessment Report; PI, Product Information; RWD, real-world data

Therapeutic area

- Drug therapeutic areas were most commonly cancer (n=11), followed by neurological conditions (n=7), and infections (n=7)

Figure 2. Therapeutic area defined for EMA EPARs containing RWE-related terminology

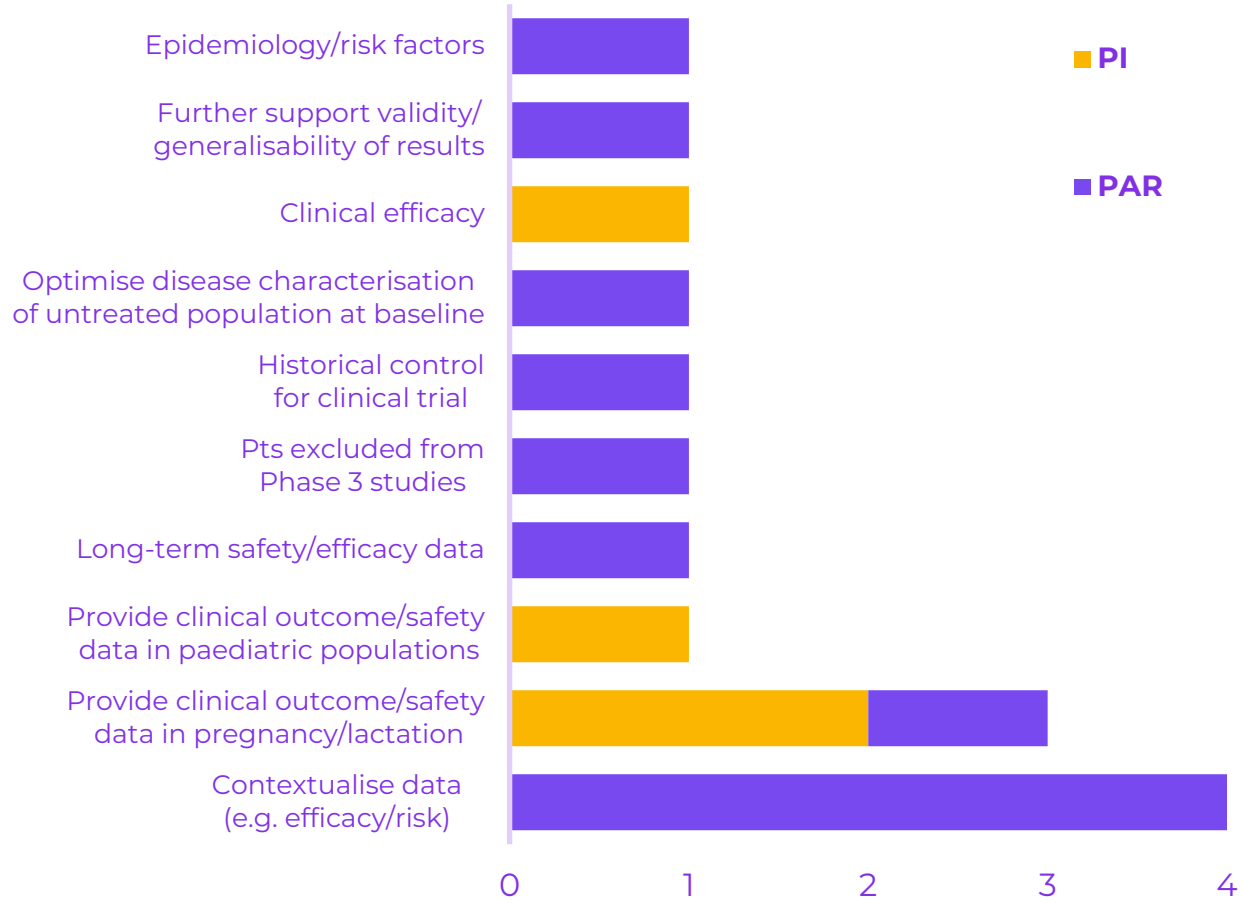


Therapeutic area defined using National Institute for Health and Care Excellence categories
Abbreviations: EMA, European Medicines Agency; EPAR, European Public Assessment Reports; RWE, real-world evidence

Reasons for providing RWD

- The most common reason reported in the PAR for providing RWD was to contextualise data
- This was often in the absence of a direct comparator in the single arm study
- In contrast, the PI focused on clinical outcome or safety data in special populations, including paediatric and pregnant populations

Figure 3. Main reasons reported in the PI or PAR for providing RWD*



* A specific PI or PAR for any drug may be included in more than one category
Abbreviations: PAR, Public Assessment Report; PI, Product Information; RWD, real-world data

Acceptability of RWD – EMA criticisms

- Within 10 PI/PAR, no criticism relating specifically to RWD was offered
- Where specified, criticisms of RWE/RWD fell into three categories:
  - study design (n=8)
  - limited population sampling (n=5)
  - use of external data sets (n=2)

*"The interpretation of data may be impacted due to **methodological limitations** of the study, including small sample size and non-randomised design".*

EMA, Hukyndra®: EPAR - Product Information[5]
EMA, Libmyris®: EPAR - Product Information[6]

*"The experience with 20vPnC in the European population is limited. Although all endpoints were met, **concerns about the intended bridge to younger cohorts remain**".*

EMA, Apexxnar®: EPAR - Public Assessment Report[7]

*"A limitation of this pool is a **lack of comparator**, therefore external data sources have been used for risk contextualisation".*

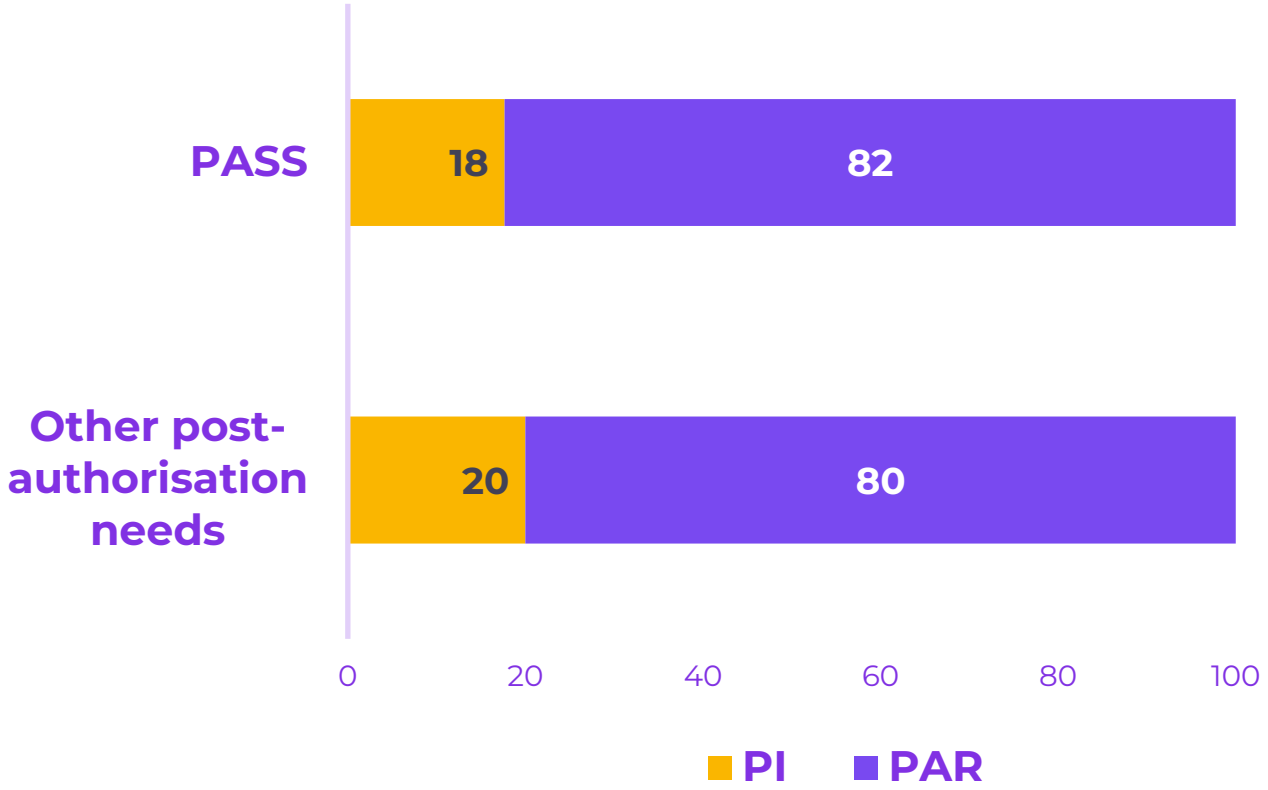
EMA, Cibinqo®: EPAR - Public Assessment Report[8]

Abbreviations: EMA, European Medicines Agency; EPAR, European Public Assessment Report; PAR, Public Assessment Report; PI, Product Information; RWD, real-world data; RWE, real-world evidence

Post-authorisation obligations relating to long-term collection of RWD (1)

- 17 documents mentioned a PASS relating to RWD/RWE:
  - 3 (18%) in the PI
  - 14 (82%) in the PAR
- 15 documents discussed other post-authorisation needs:
  - 3 (20%) in the PI
  - 12 (80%) in the PAR

Figure 4. Percentage of EMA documents that include a PASS relating to RWD/RWE, split by document type

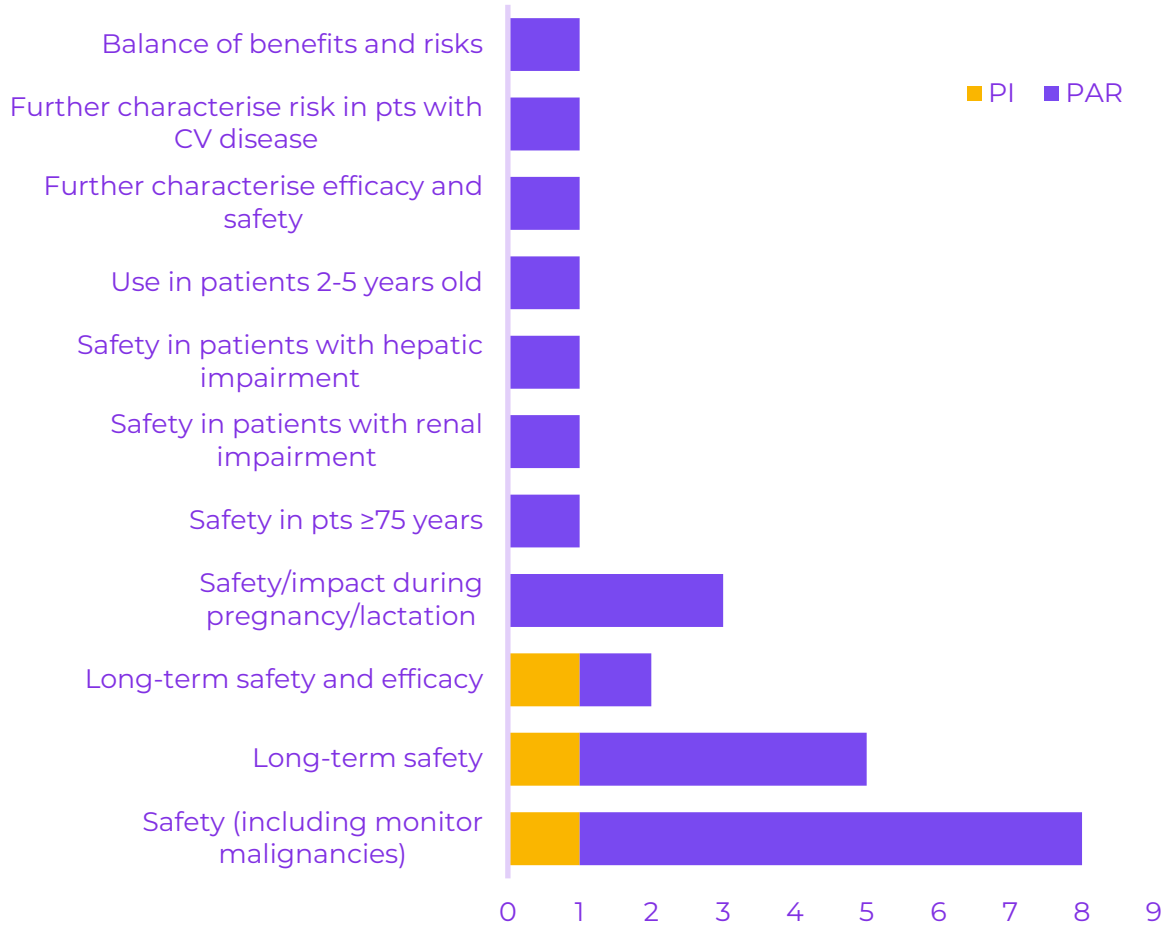


Abbreviations: EMA, European Medicines Agency; PAR, Public Assessment Report; PASS, post-authorisation safety study; PI, Product Information; RWD, real-world data; RWE, real-world evidence

Post-authorisation obligations relating to long-term collection of RWD (2)

- The specified context/need for a PASS (within the context of RWD/RWE) encompassed long-term and unspecified safety requirements
- Occasionally this was in combination with efficacy requirements
- Safety needs were also noted in specific populations:
  - The elderly
  - Hepatic or renal impaired

Figure 5. Context of PASS requirements for EMA documents that included a PASS relating to RWD/RWE*



* A specific PI or PAR for any drug many be included in more than one category
Abbreviations: CV, cardiovascular; PAR, Public Assessment Report; PI, Product Information; RWD, real-world data

Discussion

- RWE was provided to support product labelling claims in approximately one third of EMA decisions in the last year (20/06/21 - 20/06/22)

- Data were mostly reported in the supplementary PAR, not the Product Information, suggesting that the data did not significantly contribute to the regulatory decision-making

- The frequency of drugs gaining conditional authorisation indicates that large, long-term observational studies can provide valuable data, particularly in the post-authorisation period

Abbreviations: EMA, European Medicines Agency; PAR, Public Assessment Report; RWE, real-world evidence

References

[1] ISPOR 2022-2023 Top 10 HEOR Trends Report (2022) (https://www.ispor.org/heor-resources/about-heor/top-10-heor-trends) Accessed 04/10/2022

[2] Food and Drug Administration (2019) Ibrance: Multi-discipline Review (https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/207103Orig1s008.pdf) Accessed 04/10/2022

[3] European Medicines Agency https://www.ema.europa.eu/en/medicines Accessed 04/10/2022

[4] Scottish Intercollegiate Guidelines Network https://www.sign.ac.uk/what-we-do/methodology/search-filters Accessed 04/10/2022

[5] European Medicines Agency (2022) Hukyndra: EPAR – Product Information– EMEA/H/C/005548 (https://www.ema.europa.eu/en/medicines/human/EPAR/hukyndra) Accessed 10/10/2022

[6] European Medicines Agency (2022) Libmyris: EPAR – Product Information– EMEA/H/C/005947 (https://www.ema.europa.eu/en/medicines/human/EPAR/libmyris) Accessed 10/10/2022

[7] European Medicines Agency (2022) Apexxnar: EPAR – Public Assessment Report– EMEA/H/C/005451 (https://www.ema.europa.eu/en/medicines/human/EPAR/apexxnar) Accessed 10/10/2022

[8] European Medicines Agency (2021) Cibinqo: EPAR – Public Assessment Report– EMEA/H/C/005452 (https://www.ema.europa.eu/en/medicines/human/EPAR/cibinqo) Accessed 10/10/2022

Presented By

Putnam
Inizio Advisory

iNIZIO
ADVISORY

Vynamic
Inizio Advisory

Putnam
Inizio Advisory

STEM
Inizio Advisory

Research
Partnership
Inizio Advisory

Thank You!

Dr Caroline Shaw

Principal Market Access Research Scientist, Putnam PHMR

Caroline.Shaw@phmr.com

Putnam

Inizio Advisory