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PRIME-ROSE
Precision Cancer Medicine Repurposing System Using Pragmatic Clinical Trials

HPR87

Lessons learned from the Well-Established Use Pathway: a retrospective analysis

Introduction

Many medicines are widely used in clinical practice but remain off-label because regulatory approval was never sought.[1] Obtaining an on-label indication ensures formal evaluation of benefits and risks, enhances safety monitoring and may facilitate reimbursement and access. One pathway for approval is the 'Well-Established Use' (WEU) regulatory pathway, where applicants can substitute (non-)clinical studies with a comprehensive review of existing literature. The criteria to qualify for WEU are listed in box 1. This study describes the assessments of WEU applications by the European Medicines Agency, focussing on the extent of evidence of efficacy and safety.

Box 1 - Criteria for Well-Established Use[2]

- **Time over which the medicinal product has been used**
  The medicinal products must have been used for the claimed indication for at least 10 years within the EU.
- **Quantitative aspects of the use**
  The applicant must provide evidence on systematic use of the medicinal product for the claimed indication
- **Degree of scientific interests**
  The applicant must provide evidence that there is continuous scientific interest in the use of the medicinal product, reflected by published literature
- **Coherence of scientific assessments**
  The provided scientific literature must exhibit a consistent view that the medicinal product is a treatment of choice

Methods

Study design: Retrospective analysis of European Public Assessment Reports (EPARs) relating to applications submitted via the WEU pathway between 1995 and 2025

Extracted: Regulatory characteristics (e.g. approval status, orphan designation), evidence supporting the grounds for WEU and the types of evidence supporting the benefit-risk assessment.

Results

A total of 22 WEU applications were identified, of which 18 were included. Indications were diverse and the majority held orphan designation (Table 1).

- Four applications were excluded: one application had no publicly available EPAR and 3 were for radio-isotopes

Applicants used various evidence sources to demonstrate WEU (Figures 1-2).

- For time and extent of use, the most common evidence included scientific literature, named-patient/compassionate use programmes, magistral formulations, clinician or patient surveys, and treatment guidelines.

Evidence supporting benefit/risk was heterogeneous.

- Randomised clinical trials were most frequently reported (n=10), followed by retrospective cohort studies (n=8) and case series/reports (n=5). Nine applications were supported by both prospective and retrospective evidence, while only one application was supported exclusively by retrospective studies.

Four applications were withdrawn and two refused

- Reasons for withdrawal were commercial reasons (n=3), extended time needed to resolve all issues and/or questions (n=2) and inability of the CHMP to conclude a positive benefit/risk balance (n=1).
- Dropcys (mercaptamine 0.1%) and Ipique (bevacizumab) were refused; while both active substances were considered WEU. Dropcys was refused since the applicant failed to demonstrate the efficacy, safety and quality of the proposed formulation and Ipique was refused because the applicant failed to bridge the published evidence to the submitted product.

Table 1. Medicinal products included in the analysis of Well-Established Use applications

Active substance (brand name)	Therapeutic area (MeSH)
Aminosalicylic acid (Granupas)*	Tuberculosis
Arginine/lysine hydrochloride (LysaKare)	Radiation injuries
Busulfan (Busilvex)	HSCT
Caffeine citrate (Peyona, previously Nymusa)*	Apnea
Cholic acid (Orphacol)*	Digestive system disease Metabolism, inborn errors
Edotreotide (SomaKit TOC)*	Neuroendocrine tumours Radionuclide imaging
Glycopyrronium bromide (Sialanar)	Sialorrhea
Ketoconazole (Esteve)*	Cushing syndrome
Amino acids (Maapliv)*	Maple syrup urine disease
Mitotane (Lysodren)*	Adrenal cortex neoplasms
Pentosan polysulfate sodium (Elmiron)	Cystitis, interstitial
Thiotepa (Tepadina)	HSCT
Artesunate (Garsun)*	Malaria
Caffeine citrate (Blectifor)*	Bronchopulmonary dysplasia
Ketoconazole (AID-SCFM)	Cushing syndrome
Sodium benzoate (Prohippur)*	Urea cycle disorders, inborn Hyperglycinemia, nonketotic
Bevacizumab (Ipique)	Wet macular degeneration
Mercaptamine (Dropcys)*	Corneal cystinosis

Table legend. *Colours represent the authorisation status: green, approved; yellow, withdrawn and red, refused. An asterisk indicates orphan designation. Abbreviations: hematopoietic stem cell transplantation (HSCT) and Medical Subject Headings (MeSH)*

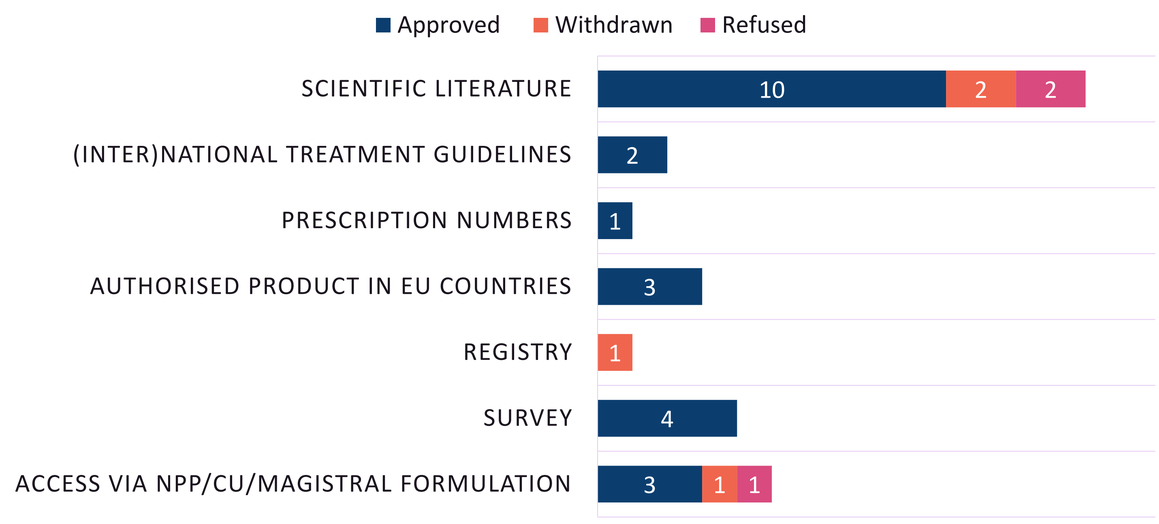


Figure 1. Evidence categories used to support the ≥10 years of use criterion in included Well-Established Use applications by authorisation status*. Abbreviations: compassionate use (CU), European Union (EU) and named-patient programme (NPP)*

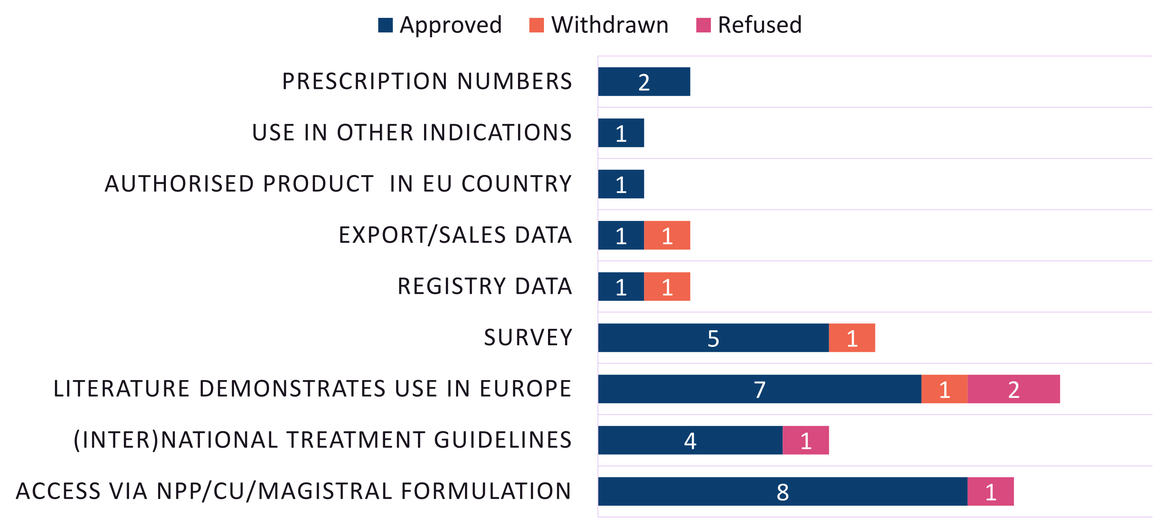


Figure 2. Evidence categories used to support the quantitative aspects of use criterion in included Well-Established Use applications by authorisation status. *Abbreviations: compassionate use (CU), European Union (EU) and named-patient programme (NPP)*

Conclusion

The WEU pathway offers a viable route for formalising marketing authorisation. Diverse evidence types can support approval, showing that this pathway can be adapted to deal with a variety of studies and evidence. These findings may inform future WEU applications.

Disclosures
The views expressed are those of the authors and do not necessarily reflect the official positions of the institutions or organisations with which they are affiliated.
The presenting author declares no competing interests related to this work

Funding
This presentation is part of work package 4 of PRIME-ROSE (Precision Cancer Medicine Repurposing System Using Pragmatic Clinical Trials), a Horizon Europe project funded by the European Union. EU Grant No. 101104269

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Co-funded by the European Union