Industry Perspective on Patient Engagement in Drug Development and Regulatory Decision Making

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Industry Perspective on Patient Engagement in Drug Development and Regulatory Decision Making

Over the last decade, patient engagement (PE) in medicines development has become increasingly normalized. In particular, the inclusion of patient experience data (PED) in the regulatory process.

Regulatory agencies and HTA bodies are progressing to incorporate the voice of the patient and patients' lived experience through the use of PED more systematically in their review and approval processes for new product submissions and value assessments.

- In 2018, 70.8% of drug application dossiers approved by the FDA (CDER) reported using PED in the drug review.
- In 2019, PED was reported as relevant for 81.3% of drugs approved in 2019 by FDA (CDER)

Source: https://patientfocusedmedicine.org/docs/Trends-in-the-Fast-Evolving-PE-PED-Landscape.pdf

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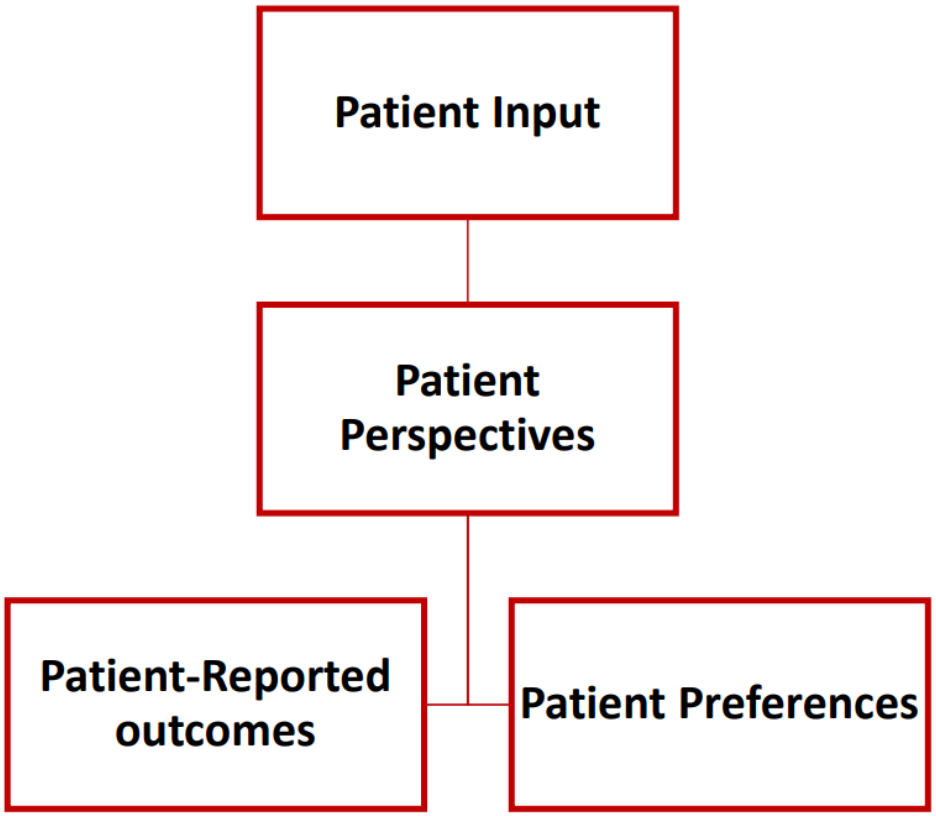
Industry's contribution to Patient Engagement Science



- **Patient Input**: includes a wide range of information and perspectives such as anecdotal comments, testimony, patient opinions expressed publicly etc.
- **Patient Perspectives**: includes information relating to patients' experience with a disease or condition and its management
- **Patient Reported Outcomes**: any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response
- **Patient Preferences**: Qualitative or quantitative assessments of the relative desirability or acceptability to patients of specified alternatives or choices among outcomes or other attributes that differ among alternative health interventions

Source: https://www.fda.gov/media/146925/download and https://www.fda.gov/media/92593/download

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Patient Preferences vs. PRO

Both are reported by patients, but:

Patient Preference	PRO
Qualitative or quantitative assessments of the relative desirability or acceptability to patients of specified alternatives or choices among outcomes or other attributes that differ among alternative health interventions	***Any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response***
PP study would address whether a patient would be willing to choose a treatment that causes a specified level of reduction (i.e., loss) in physical function in exchange for a specified improvement (i.e., gain) in pain relief	Two widely used PRO measures are the Visual Analogue Score (VAS) for pain and the Health Assessment Questionnaire (HAQ) and Disability Index (DI) score for physical function

Source: https://www.fda.gov/media/92593/download

Patient Reported Outcomes – PROs

PROs as clinical outcome assessments in clinical development.

- **Established PROs** can be used in clinical development and regulatory decision making
  - *Example: HRQoL questionnaires*
- **Novel PROs** need to be validated/qualified prior to implementation in regulatory decision making.
  - *Example: PROactive*

Regulatory pathway for including PROs in clinical development and regulatory decision making:

- As part of a Scientific Advice for a specific medicinal product
- In case of novel PRO: **Qualification of Novel Methodologies**
  - Challenges: Long timelines (years) and specific expertise required
- Inclusion of PROs in MAA -> PROs are reflected in the EPAR and sometimes in the EU-PI

Source: https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/qualification-opinion-proactive-chronic-obstructive-pulmonary-disease-copd_en.pdf and https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-advice-protocol-assistance/qualification-novel-methodologies-medicine-development-0

Patient Preferences - PP

PP data can provide valuable information about

- Which **benefits and risks** are *most important* to affected patients
- What benefit-risk tradeoffs *are acceptable* from the patient perspective
- *How do these patients think about these tradeoffs*
- Are there *clinically-relevant subgroups of patients* that would accept a particular benefit-risk profile and/or choose one treatment option over other alternative

Regulatory pathway for including Patient Preference Studies in clinical development and regulatory decision making:

- As part of Scientific Advice for a specific medicinal product
  - Note: currently no separate scientific advice pathway in particular for patient preference studies
- Qualification of Novel Methodologies for patient preferences methodologies
  - E.g. IMI PREFER
- Inclusion of PP data in MAA is up to the applicant, no specific EU guidelines *yet*
  - ➢ Currently no EU guideline on the role of PP in regulatory decision making, PP are not specifically reflected in the EPAR and EU-PI
  - ➢ Currently PP study design methodology is not part of an EU guideline

Reference: https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/ema-regulatory-science-2025-strategic-reflection_en.pdf

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Patient Preferences & Regulatory Decision Making: an Example

Patient preferences for ketamine-based antidepressant treatments in treatment-resistant depression: Results from a clinical trial and panel

Angelyn O. Fairchild[a], Eva G. Katz[b], Shelby D. Reed[a,c,*], F. Reed Johnson[a,c], Allitia DiBernardo[d], David Hough[d], Jaskaran Sing[e], Bennett Levitan[d]

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A **discrete-choice survey** was conducted amongst trial participants and treatment-naïve panelists **to evaluate relative importance of benefits and harms associated with treatment** and **to quantify the maximum acceptable risk** patients would accept for treatments that relieved depression.

Source: https://link.springer.com/article/10.1007/s43441-021-00340-6, https://www.sciencedirect.com/science/article/pii/S0941950020300348, https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/211243Orig1s000MedR.pdf

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Transparency of Patient Experience Data (PED at FDA)

Sponsor

Patient-preference and PRO data, which addressed key elements of patient-experience data requested by the FDA, were integrated into the SPRAVATO® NDA as illustrated in the common technical document triangle

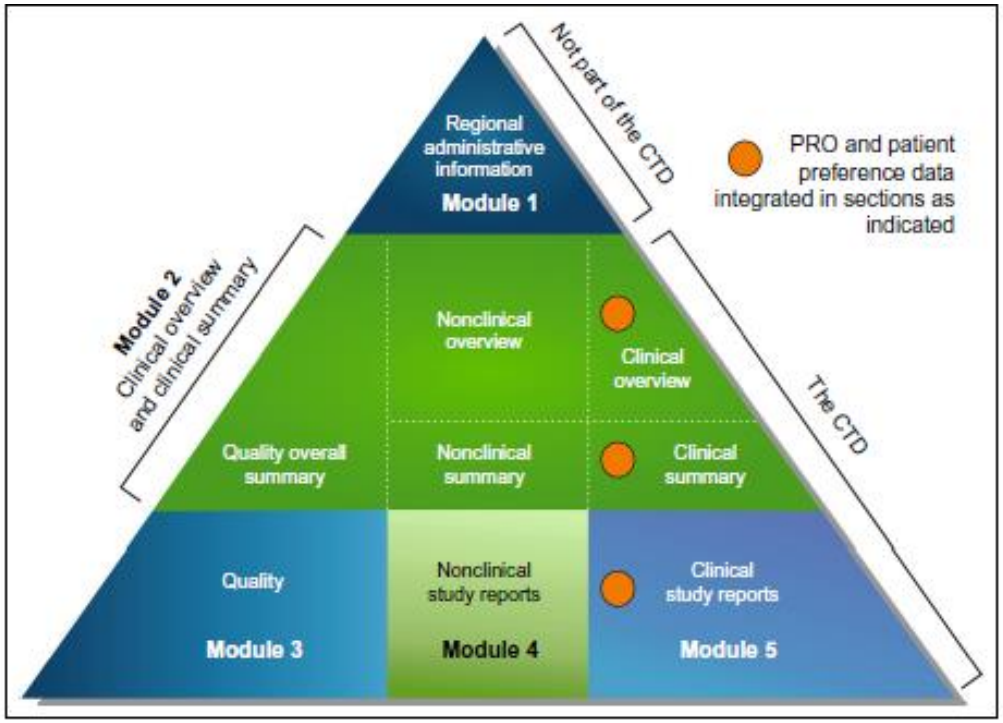

Fig. 2 Integration of patient-reported outcomes and patient-preference data into Esketamine NDA submission, shown using CTD triangle. *CTD* common technical document

Source:https://link.springer.com/article/10.1007/s43441-021-00340-6

Transparency of Patient Experience Data (PED at FDA)

Regulator - FDA

FDA review of the esketamine NDA was posted on in July 2019, which included the completed patient-experience checklist and extensive discussion on the PRO and preference work

- The FDA used the patient-experience data, including individual testimony, feedback from patient advocacy groups, and PRO measures from the clinical trials as part of their assessment to support clinical efficacy of esketamine + AD in TRD

1.3. Patient Experience Data

Patient Experience Data Relevant to this Application

☒	The patient experience data that was submitted as part of the application include:			Section where discussed, if applicable
	☒	Clinical outcome assessment (COA) data, such as		6.1 (Study Endpoints), 6.2, 6.3, 6.4
		☒	Patient reported outcome (PRO)	
		☒	Observer reported outcome (ObsRO)	
		☒	Clinician reported outcome (ClinRO)	
		☒	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Natural history studies		
	☒	Patient preference studies (e.g., submitted studies or scientific publications)		7.2 Other Efficacy Considerations
	☐	Other: (Please specify)		
☒	Patient experience data that were not submitted in the application, but were considered in this review:			
		☒	Input information from participation in meetings with patient stakeholders (Patient Focused Medical Product Development Meeting (Depression and Bipolar Support Alliance), November 16, 2018)	2.1 Analysis of Condition
		☐	Patient-focused drug development or other stakeholder meeting summary reports	
		☐	Observational survey studies designed to capture patient experience data	
		☐	Other: (Please specify)	
☐	Patient experience data was not submitted as part of this application			

ig. 3 Patient-experience checklist from the FDA's clinical review of esketamine NDA

Reference:

1. https://link.springer.com/article/10.1007/s43441-021-00340-6
2. https://www.sciencedirect.com/science/article/pii/S0941950020300348
3. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/211243Orig1s000MedR.pdf
4. https://www.nejm.org/doi/10.1056/NEJMp1903305

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Patient Engagement = Hot Topic In The EU!

Importance of patient perspectives in drug development

- Regulatory Science Strategy (RSS) to 2025 includes reinforcing patient relevance in evidence generation
- January 2021 pilot for early interactions with patients and consumer organizations
  - Involve patients and consumers at start of the evaluation of new MAAs to share their experience and concerns about condition(s) and key aspects that are important for them to be considered during assessment
- ICH Reflection Paper on Patient-Focused Drug Development proposed by both EMA and FDA and endorsed by the ICH Assembly in June 2021.
- December 2021 Regulatory Science Research Needs initiative
  - Standards for PROs and patient preferences to inform regulatory and HTA decisions
  - Optimal approaches for patient input into the benefit-risk assessment
  - Methodologies to systematically gather and use patient data
  - Standards and quality requirements for designing, conducting, analyzing, and reporting PRO studies and PPS for regulatory submission
- February 2022 Framework for Engagement between EMA and patients an consumers
  - Promote the generation, collection and use of evidence-based patient experience data for benefit-risk decision-making
- CHMP Work Plan for 2022 includes work to facilitate the collection and use of PED to be considered in benefit-risk evaluations
  - Multi-stakeholder workshop: Patient experience data in medicines development and regulatory decision-making | European Medicines Agency (europa.eu)

Multi-stakeholder workshop: Patient experience data in medicines development and regulatory decision-making

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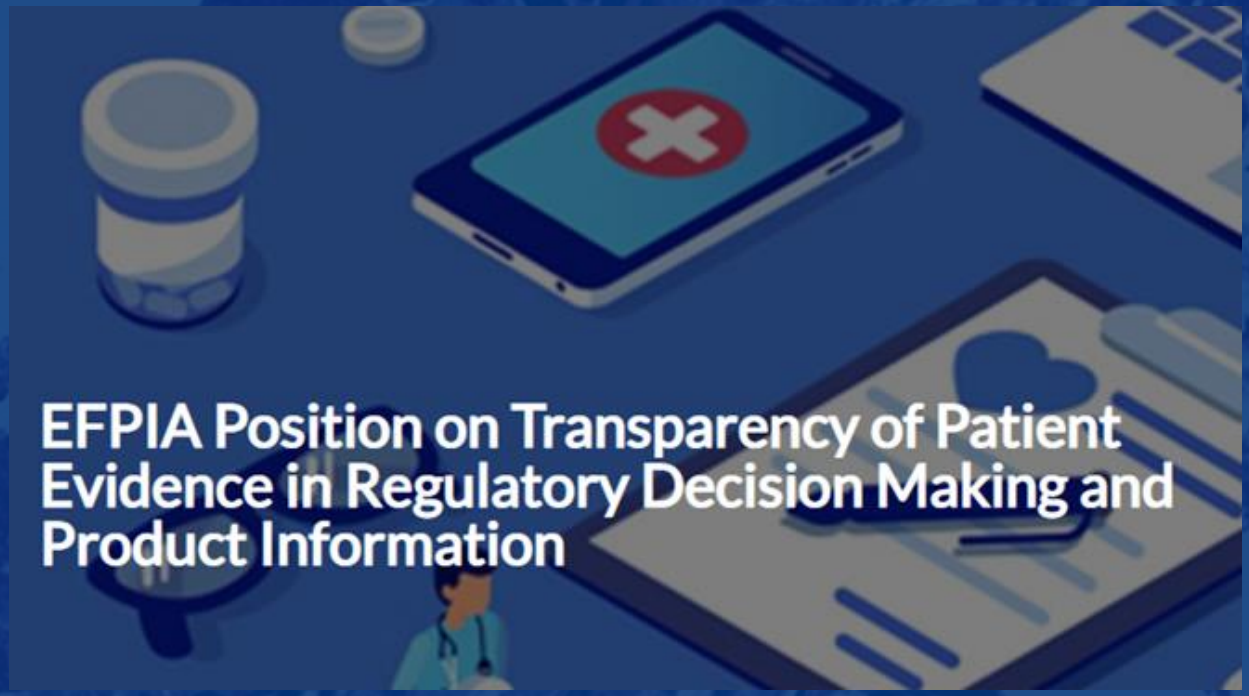
Date: 21/09/2022

Location: European Medicines Agency, Amsterdam, the Netherlands

Conclusions

Many ongoing initiatives in the PED space from a variety of interested stakeholders, including regulators

- While there is increased interest and expectation that PE and PED are utilized during drug development there is a lack of clear guidance and understanding on how PED is being considered by regulators and utilized in their regulatory decision-making including benefit-risk assessments and labeling



Viral exacerbation at 40x magnification

Source: EFPIA Position on Transparency of Patient Evidence in Regulatory Decision Making and Product Information

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Back-up

Viral exacerbation at 40x magnification

Publications on Qualification Procedures

- Biomarker Qualification at the European Medicines Agency: a review of Biomarker qualification procedures from 2008 to 2020
  - Bakker et al: Biomarker Qualification at the European Medicines Agency: A Review of Biomarker Qualification Procedures From 2008 to 2020 (wiley.com)
  - Berman et al: Biomarker Qualification at the European Medicines Agency: A Look Under the Hood: Biomarker Qualification at the European Medicines Agency: A Look Under the Hood (wiley.com)
- Biomarkers in medicines development – from discovery to regulatory qualification and beyond
  - Hendrikse et al: Biomarkers in Medicines Development—From Discovery to Regulatory Qualification and Beyond (nih.gov)
- Biomarkers: Gromova et al: Biomarkers: Opportunities and Challenges for Drug Development in the Current Regulatory Landscape (sagepub.com)
- Perspectives on statistical strategies for the regulatory biomarker qualification process
  - Hendrix et al: bmm-15-669.pdf (nih.gov)
- The European Medicines Agency experience with biomarker qualification
  - The European Medicines Agency experience with biomarker qualification - PubMed (nih.gov)
- Regulatory Experience of Biomarker Qualification in the EMA
  - Regulatory Experience of Biomarker Qualification in the EMA – ScienceDirect

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