Patient-focused drug development: Increasing activity in the US and the EU

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Abstract
Increased patient engagement in medicine development and regulatory approval decisions is occurring at a time when pharmaceutical companies and regulatory agencies are formalising the processes and considerations for this engagement. This article describes framework and standard building efforts in the EU and US with an eye towards advancing a global approach across the medicine lifecycle, including how the pharmaceutical industry is preparing to use patient experience data when developing medicines and in support of marketed medicines. This article looks at how such increasing activity may impact how medicines are developed and maintained on the market.

Introduction

Patient-focused drug development (PFDD) is a term commonly used to describe a systematic approach to ensure that patients' experiences, perspectives, needs and priorities are captured and meaningfully incorporated into medicine development and (regulatory/health authority) evaluation throughout the medicine lifecycle.[1] As experts in what it is like to live with their condition, patients are uniquely positioned to inform the understanding of their disease and its treatment context across the medicine lifecycle.

The European Medicines Agency (EMA) and US FDA are supportive of, and in the case of the FDA, formalising some of the key PFDD concepts through which the patient voice can be incorporated into the regulatory oversight of medicine development and review as follows:

- Facilitating and advancing use of systematic approaches to collection and utilisation of robust and meaningful patient and caregiver input to more consistently inform medicine development and regulatory/health technology assessment (HTA) body decision-making.
- Encouraging identification and use of approaches and best practices to facilitate patient enrolment and to minimise the burden of patient participation in clinical trials.
- Enhancing understanding and appropriate use of methods to capture information on patient preferences and the potential acceptability of tradeoffs between treatment benefit and risk outcomes.
- Identifying the information that is most important to patients related to treatment benefits, risks, and burden, and how to best communicate the information to support shared patient and healthcare provider decision-making.

Figure 1 outlines types of patient experience data (PED) and when and how PED can be applied during a medicine's lifecycle. This graphic is not inclusive of all types of PED, but is intended to illustrate how pharmaceutical companies and health authorities might consider patient input throughout medicine development, regulatory review of a marketing application, and once the medicine is available on the market.

In addition to PFDD activities being undertaken by EU and US regulators, there are multiple complementary activities under the direction of patient-centred organisations around the globe. A few notable efforts include initiatives to:

- Develop a pragmatic "Points to Consider" about patient involvement in various activities throughout the product lifecycle under the Council for International Organizations of Medical Sciences (CIOMS)[2]
- Improve the framework for patient engagement via the EU Innovative Medicines Initiative (IMI)[3]
- Coordinate existing patient-focused activities under Patient-focused Medicines Development (PFMD)[4]
- Identify and implement best practices for integrating the patient voice into the conduct of research and healthcare decision-making by the US National Health Council (NHC)[5]
- Drive adoption of methods by which patients' perspectives shape processes for discovering, developing and delivering medicines under the US Faster Cures initiative.[6]

Within pharmaceutical companies, research and development activities focus on conducting ground-breaking science to bring innovative medicines to patients who need them around the globe. New medicines are developed via global development programmes to satisfy the regulatory requirements of multiple health authorities. This is highly relevant for the topic of PFDD, where pharmaceutical companies seek to leverage framework and standards building in the US with scientific method and patient engagement framework development in the EU to advance a global approach that better captures PED across the medicine lifecycle and is ultimately fit to support regulatory and HTA body decisions.

Hence, this article will provide an overview of PFDD focusing on key activities in the EU and US, highlighting distinct and complementary approaches, and how the pharmaceutical industry is preparing for this new perspective when developing medicines and refining on-market medicines.

Figure 1: Examples of utilisation of PED throughout the medicine lifecycle.

	Research & discovery	Preclinical development	Clinical development (Phase I to III)	Marketing authorisation/health technology assessment (HTA)	Post-marketing
PED examples & use	• Current treatment experience • Unmet need characterisation • Initial influence on treatment design	• Natural history • Disease/ treatment burden • Input on trial protocol design, assessed outcomes & logistics • Further treatment design input • Clinical trials: improved data quality • Recruitment & retention	• Natural history • Disease/treatment burden • Patient treatment preferences and risk tolerance • Input on trial protocol design, assessed outcomes (including patient reported outcomes and quality of life) & logistics • Subpopulation identification • Mitigation of risk • Treatment arm selection • Biomarker selection • Eligibility for expedited pathways, eg, EMA PRIME	• Patient treatment preferences and risk tolerance • Assessment of clinical outcomes Regulatory or HTA decision making support, eg: • Dose selection • Formulation • Benefit–risk assessment • Labelling content and wording • Assessment of value	• Perspectives on clinical practice and living with a disease • Assessment of clinical outcomes • Patient support programme (PSP) development • Communication of benefit–risk • Labelling optimisation/ expansion

Patient-focused drug development in the EU

Facilitation of patient engagement in medicines development and in supporting access to those medicines is a longstanding topic in the EU and the EMA has an established framework for engaging with patients, consumers and patient organisations.[7] Patient representatives are also included on every EMA Committee, covering scientific advice, paediatric development, assessment of marketing authorisation applications and ongoing safety monitoring among others. At a national level, EU patients are also often engaged at the HTA appraisal stage, as participants in committees or providers of submissions to HTA bodies making decisions that impact patient access.

However, it is clear there is a desire from patients (and the groups that represent them), industry, regulators and HTA bodies to better engage patients at all stages of the medicine lifecycle, but significant challenges remain before the potential of this interaction can be fulfilled. Key challenges include addressing the need for established regulatory/HTA body guidance, qualified methodologies to capture patient preferences, and a robust and consistent framework to engage patients in PFDD activities.

Patient engagement in medicine development is the subject of active discussion in Europe, often under IMI. IMI is Europe's largest public-private initiative, between the EU, represented by the European Commission and the pharmaceutical industry represented by the European Federation of Pharmaceutical Industries and Associations (EFPIA). IMI aims to speed the development of better and safer medicines for patients and three key IMI (or IMI-initiated) activities specifically relate to PFDD and are outlined below:

- **Training a wider pool of patient experts – EFO EUPATI.** The need for patient input across the medicine lifecycle is clear, but accomplishing this requires patients and their representatives to engage in complex scientific discussions within a highly regulated legislative framework. It can be challenging for patients to engage and advocate without a certain level of scientific and regulatory knowledge. The initial IMI European Patients' Academy on Therapeutic Innovation (EUPATI)[8] ran from 2012 to 2017 and was a European project implemented as a public-private partnership by a consortium of pharma, academia, not-for-profit, and patient organisations. EUPATI trained more than 100 patient experts on medicine development, clinical trials, medicine regulation and HTA review, offered and maintained Toolbox on Medicine Development, and coordinated a network of national platforms for patient advocates. The value of the project was widely recognised and EUPATI's work continues to be IMI funded, but is now under the leadership of the European Patients Forum (EPF), with the updated name of "Ensuring the Future Of" (EFO)-EUPATI.[9]
- **Methodologies and guidance on patient preference elicitation for regulatory and HTA decision-making – IMI PREFER.** At present, despite wide interest in patient preferences, there are no qualified methods for the elicitation of patient preferences for use by industry, regulator or HTA/reimbursement decision-makers or guidance on how to use these data in these settings. Patient experience is often shared as anecdotes rather than supported by data generated via rigorous scientific methods. The availability of rigorous patient preference data can facilitate impactful decisions, such as:
  - Disease experience: Better understanding of a disease, including what disease impacts are most important to patients, challenges of current treatments, tolerance of risks, and patient sub-group variability
  - Patient defined endpoints: Inclusive of patient reported outcomes (PROs), key symptoms, and overall value of the medicinal product from a patient perspective
  - Benefit–risk trade-offs: Use of scientific methodologies to more robustly incorporate patient preferences in important decisions in medicine development, including acceptable risks and harms given uncertainties, how these vary by patient group, and optimising dosing, routes of administration, and treatment duration

Figure 2: Outlines of discrete choice experiment and best–worst scaling methodologies.

These methods were established in fields such as economics but both are increasingly used to elicit patient preferences during medicine development. Please note that both examples below are highly simplified and for illustrative purposes only.

Discrete choice experiment example

Discrete choice experiments identify the probability that an individual chooses an option among a set of alternatives. In practice, we cannot know all factors affecting individual decisions as their determinants are partially observed or imperfectly measured.

For a hypothetical preventative screening programme in oncology			
Feature	**Option 1**	**Option 2**	**Option 3**
Testing option	Scan	Scan and biopsy	Given these options I would not get screened
Procedure time	30 minutes	2 hours	
Discomfort	None-mild	Moderate	
Travel time	30 minutes	1.5 hours	
Accuracy	90%	99%	
Choose one of the three options			

Best–worst scaling example

Best–worst scaling is when respondents are shown a subset of items from a master list and are asked to indicate the best and worst items (or most and least important, or most and least appealing, etc).

For a new treatment in oncology		
Least important	**Attribute**	**Most important**
	Activities of daily living: able to go back to work part time	
	Length of life: increase of 3 months	
	Treatment administration: moderate discomfort	
	Treatment duration: 4 weeks	
	Side effects: improved tolerability compared with standard of care	
	Route of administration: intravenous vs pill	
Choose the single most and the single least important attribute to you		

- Clinical trial design: Design and execution aspects to make trials more accessible (eg, ensuring practical considerations) and finding ways to effectively share results.

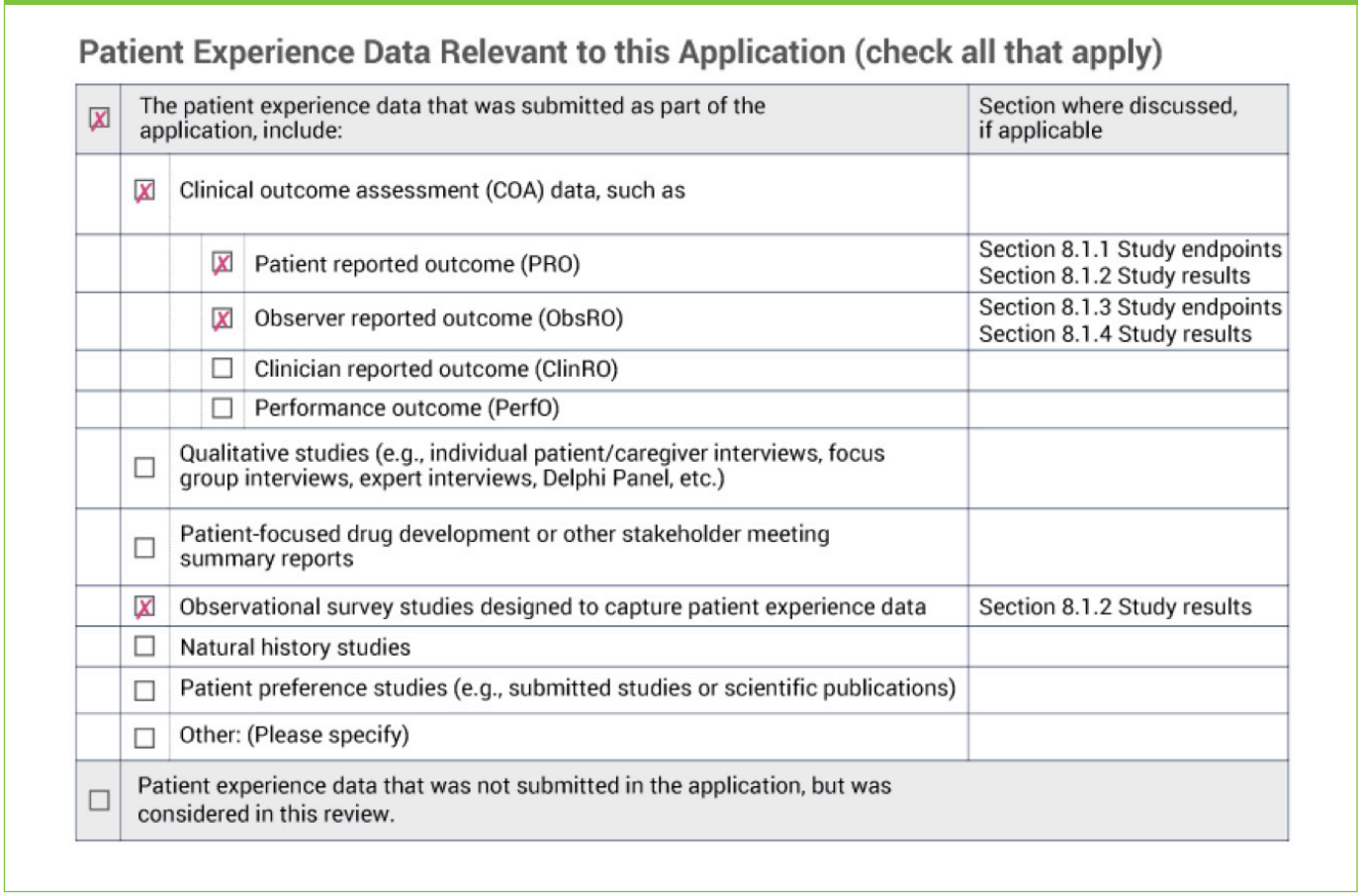
The IMI Patient Preferences in Benefit–Risk Assessments during the Drug Lifecycle (PREFER) project is a five-year project which started in 2017. The project aims to develop recommendations to support guidance development on how and when to include patient preferences on benefits and risks of medical products for industry, regulator, and HTA/reimbursement decisions.

The development of evidence-based recommendations through IMI PREFER could have a transformative impact on the medicine lifecycle. The impact would be significant even if just the best understood approaches such as Discrete Choice Experiments (DCE) and/ or Best–worst Scaling (BWS) were qualified by a regulator such as the EMA. See Figure 2 for a simplified outline of these methodologies. The IMI PREFER work continues and we look forward to the outputs in 2021.

- **A consistent framework for engaging patients in key decision-making – IMI PARADIGM.** The IMI project called Patients Active in Research and Dialogues for an Improved Generation of Medicines (PARADIGM), aims to provide a framework that enables structured, effective, meaningful, ethical, innovative, and sustainable patient engagement.[10] It will develop processes and tools for three key decision-making points: research priority setting, design of clinical trials, and early dialogue. PARADIGM will integrate the needs, perspectives and expectations of patients (including vulnerable populations) involved and will also produce a set of metrics to measure the impact of patient engagement. IMI PREFER and IMI PARADIGM activities are complementary and a Memorandum of Understanding (MOU) was recently published for both initiatives.[11] The purpose of the MOU is to enhance cooperation and collaboration, to avoid duplicate efforts and maximise results.

In addition to the EU PFDD activities described above, it is important to monitor international developments, particularly in the US where PFDD is also very active. EU and US regulators are working closely on this topic and the FDA and EMA have recently formed a patient engagement cluster[12] to share best practices.

Figure 3: Patient experience data relevant to an FDA marketing application.



Patient Experience Data Relevant to this Application (check all that apply)

☒	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		
		☒	Patient reported outcome (PRO)	Section 8.1.1 Study endpoints Section 8.1.2 Study results
		☒	Observer reported outcome (ObsRO)	Section 8.1.3 Study endpoints Section 8.1.4 Study results
		☐	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		Section 8.1.2 Study results
	☐	Natural history studies		
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		
	☐	Other: (Please specify)		
☐	Patient experience data that was not submitted in the application, but was considered in this review.			

Patient-focused drug development in the US

PFDD was codified by the US Congress in Section 3002/Title III of the 21st Century Cures Act[13] and included in the fifth and sixth iterations of the Prescription Drug User Fee Acts (PDUFAs V[14] and VI[15]).

21st Century Cures Act and patient experience data. The 21st Century Cures Act mandated that FDA establishes a framework relating to the collection of PED and how such data could be used in medicine development and regulatory decisions. The framework should cover:

- How persons wishing to propose draft guidance to FDA may submit documents
- The format and content for PED submissions to FDA
- The process for FDA response to the submission of patient experience data outside of an application.

For all approved applications submitted after June 2017, FDA is required to include a brief statement regarding any PED and related information that was submitted and reviewed for that application. This information currently takes the form of a tabular presentation to satisfy the requirement of a "*brief statement regarding the patient experience data and related information, if any, submitted and reviewed as part of such application*." To generate this table, FDA has requested sponsors to *"include a summary table with patient experience data type and reference the section in the application where the data is described in detail*." Genentech's haemophilia A treatment Hemlibra was among the first products to include this new dedicated section on patient experience data in FDA review documents (see Figure 3).

PDUFA V and VI and patient experience data/PFDD

Under PDUFA V,[16] FDA held more than 20 PFDD meetings in specific diseases to address the need for more systematic collection of direct patient input or PED. These meetings highlighted that what patients care most about may not be measured in clinical trials or reflected in medicinal product labelling.

Under PDUFA VI,[17] FDA is now charged with establishing a public registry of tools and holding stakeholder meetings in advance of issuing four guidances to address, in a stepwise manner, how stakeholders can collect and submit PED that is fit for regulatory decisions. These four guidances take advantage of PDUFA V learnings and tie into the Agency's benefit–risk assessment framework. The guidances are expected to be finalised by 2021 and expected to describe systematic approaches to collect and use patient inputs to inform medical product development and bridge from PDUFA V to VI and to cover:

1. Comprehensive and representative patient and caregiver data collection
2. Processes and approaches to determine most important impacts to patients
3. Measuring disease impact to facilitate meaningful patient input in clinical trials
4. Revise or supplement guidance on PRO measures and address the incorporation of clinical outcome assessments into endpoints.

Also under PDUFA VI, FDA is to hire 64 dedicated experts covering clinical, statistical, psychometric, health economics and outcomes research (HEOR) aspects within its review divisions who work with

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patients, patient advocacy groups and other stakeholders to advance the science of patient input, including the use of PRO measures. While the FDA is focusing on practical approaches and methods of gaining patients perspectives, activity in the EU is complementary, particularly the work of IMI PREFER that is focusing on development of recommendations on how and when to include patient preferences on benefits and risks of medical products for industry, regulator or HTA/ reimbursement decision-making, including potential regulator qualification of selected methodologies.

In June 2018, FDA issued the first of the four guidance documents, "*Collecting Comprehensive and Representative Input*",[18] focusing on from "whom and how" to collect representative patient input and how to submit PED to inform medicine development and regulatory decision-making. This draft guidance presents key concepts inclusive of sampling methods and operational concepts; a glossary of terms is also included.

How industry is preparing to use PED

In parallel with the extensive external activity on the topic, it is important for the multiple functional departments within pharmaceutical companies to collaborate to advance from talking about PFDD and sporadic engagement to robust operational implementation of a PFDD framework. PED may not need to be generated for every medicine, but it will be important for companies to consider a consistent evidence generation approach that is inclusive of PED, ensuring that PED is captured in a timely manner for those treatments where it is relevant.

In order to develop operational processes for implementing PFDD, many parts of a company must leverage the knowledge that resides across departments. For example, the regulatory affairs and regulatory policy functions may be most familiar with evolving PFDD concepts as described by the health authorities. The scientific expertise of social and behavioural scientists can positively influence an evolving regulatory and scientific policy environment and raise awareness of how best to generate PED. Clinical development, project management, pharmacovigilance, medical affairs, and commercial (eg, market access) functions should also be involved.

Pharmaceutical companies are increasingly building groups with expertise in gathering patient experience data (eg, patient-focused centres of excellence) or partnering with vendors that do so. These experts are piloting and conducting studies to generate PED to be applied to dose selection, formulation preferences, and benefit–risk tradeoffs, which may also support regulatory and HTA decisions for new medicines. These pilot opportunities will provide companies with a better understanding of how they may engage with health authorities to gain feedback on study design, identify critical opportunities to communicate with regulators/ HTA bodies/patients, and finally work in partnership to map a communication plan by which to share results with patients and healthcare providers as they participate in shared decision-making conversations at the point of care.

Conclusions

The development of medicines and the healthcare systems that deliver them to patients are constantly evolving and have changed significantly over the decades. Patients expect, and are increasingly empowered to, engage more broadly in the development of medicines, to comment on their use and want a greater say in treatment decisions. Pharmaceutical companies, regulators, and HTA bodies must continue to build partnership-working with patients to develop the medicines that meet their needs.

We may soon be able to realise the benefits that PFDD has to offer the patients who take the medicines we develop. Success depends on active engagement by the pharmaceutical industry in multi-stakeholder PFDD discussions (eg, in the EU and US), considering how best to operationalise PFDD within a company, and in gaining learning from PFDD via pilots. All stakeholders must work together to move PFDD from a theoretical concept to practical reality. New medicines must serve patient needs and patients are uniquely positioned to advise and inform pharmaceutical sponsors and regulators on their development and use.

References

1. US FDA. Available at: www.fda.gov/Drugs/DevelopmentApprovalProcess/ucm610317.htm
2. CIOMS. https://cioms.ch/working_groups/working-group-xi-patient-involvement/
3. IMI. Available at: https://imi-paradigm.eu/
4. Patient-focused Medicines Development. Available at: http://patientfocusedmedicine.org/
5. US National Health Council. Available at: www.nationalhealthcouncil.org/public-policy/patient-engagement
6. US Fastercures Initiative. Available at: www.fastercures.org/programs/patients-count/
7. EMA. Available at: www.ema.europa.eu/ema/index.jsp?curl=pages/partners_and_networks/general/general_content_000317.jsp&mid=WC0b01ac058003500c
8. EUPATI. Available at: www.eupati.eu/
9. EUPATI. Available at: www.eupati.eu/closing-report-eupati-2012-2017/#_Toc484713041
10. IMI. Available at: https://imi-paradigm.eu/
11. IMI. Available at: www.imi-prefer.eu/news/news-item/?tarContentId=733732
12. US FDA. Available at: www.fda.gov/ForPatients/PatientEngagement/ucm507907.htm
13. US FDA. Available at: www.fda.gov/RegulatoryInformation/LawsEnforcedbyFDA/SignificantAmendmentstotheFDCAct/21stCenturyCuresAct/default.htm
14. US FDA. Available at: www.fda.gov/forindustry/userfees/prescriptiondruguserfee/ucm272170.htm
15. US FDA. Available at: www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm446608.htm
16. US FDA. Available at: www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm
17. US FDA. Available at: www.fda.gov/forindustry/userfees/prescriptiondruguserfee/ucm446608.htm
18. US FDA. Available at: www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM610442.pdf