2021

PATIENT CENTRICITY AND SCIENCE OF PATIENT INPUT

A Position Paper prepared by the EUCOPE Regulatory Working Group

EUCOPE
European Confederation of Pharmaceutical Entrepreneurs AISBL

EUCOPE

European Confederation of
Pharmaceutical Entrepreneurs AISBL

21 May 2021

EUCOPE POSITION PAPER: PATIENTS CENTRICITY AND SCIENCE OF PATIENT IMPUT

In the recent years, patients have become increasingly involved and engaged in efforts to inform and improve drug development. In turn, the patient-focused drug development (PFDD) landscape has evolved globally, and has led to significant efforts from various stakeholders, including regulators, to incorporate the patient's voice into drug development and regulatory decision-making (see Annex I). This global focus has provided stakeholders with the understanding of the importance of the patient's unique perspective and it's potential to highlight key needs, and challenges in defining meaningful treatments.

Patient input provides valuable insights on various aspects of drug development including: inform target product profile, enhanced understanding of disease, its impact on patients and treatment burden, considerations related to clinical trial design and selection of meaningful endpoints, and improved understanding of patient's perspectives on a product's benefits and risks to inform the benefit-risk assessment. *Figure 1* illustrates timepoints during the stages of development when patient input may be beneficial.
EMA has made great strides in enhancing the incorporation of patient input into regulatory decision-making, particularly through its patient engagement efforts, by

- including patients in various EMA advisory committees.
- newly proposed one-year pilot to engage with patients and consumer groups early on during CHMP's evaluation of MAAs for Orphan products.

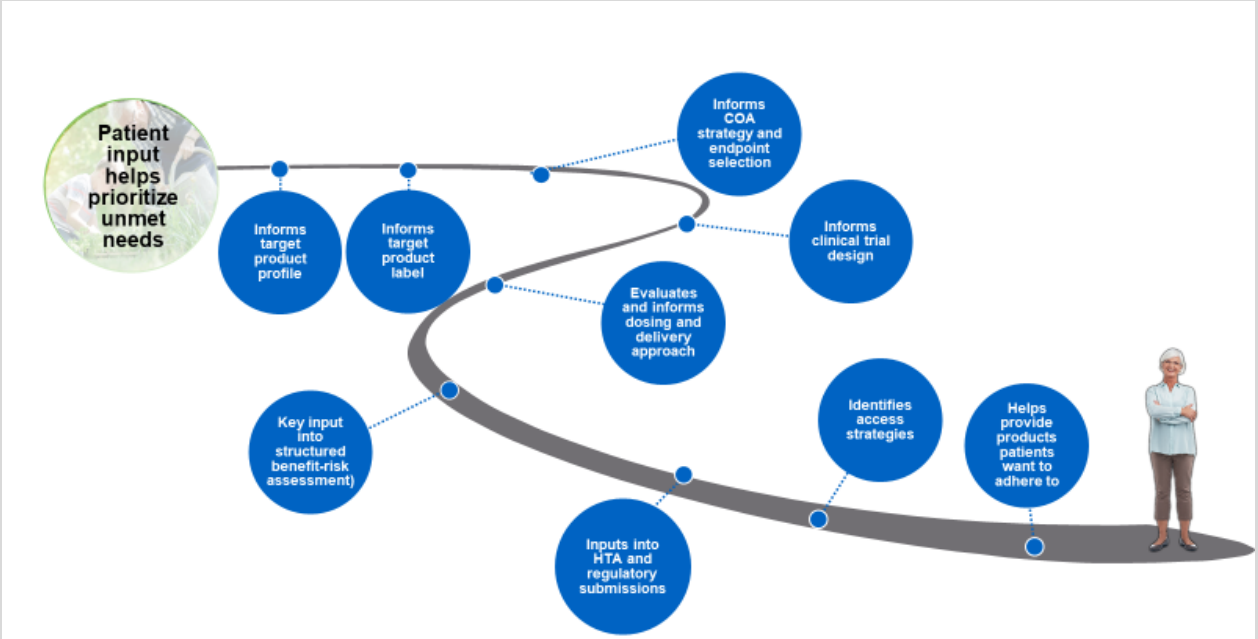
EMA's Regulatory Science Strategy 2025 also highlights EMA's commitments to further advance patient-focused drug development, focusing on both patient engagement and the "science of patient input."

OUR CONSIDERATIONS AND RECOMMENDATIONS

As described above, engagement with patients, can help inform (among other things) trial design, development and selection of COAs and related endpoints, and even the benefit-risk assessments, potentially impacting labelling or patient communication. Although recent years have seen a shift in understanding from stakeholders on the importance of this input, there still remains a need to establish regulatory confidence in the patient input and enhance quality and reliability in the collected patient experience data to inform regulatory decision-making. There is also a need to clearly define how and when (at what stage) to engage patients.
To build on existing efforts and help advance EMA's RSS 2025 goals, EUCOPE would like to propose key considerations and recommendations on two main areas: **Patient Engagement** and the **"Science of Patient Input"**.

The "science of patient input" refers to systematic collection and incorporation of methodologically-sound, robust, fit-for-purpose patient input/patient experience data throughout the drug development lifecycle. To ensure that the data is reliable and good quality and can be used as evidence for drug development and regulatory decision-making, fit-for-purpose methods, approaches, and tools for collecting and incorporating the patient input should be developed and implemented.

Figure 1: Patient input at different stages of development



Target product profile (TPP) and Target product label (TPL): The TPP is a critical place to incorporate direct patient input to maximize the value of medicines, improve patient experience, and drive meaningful differentiation.

Target product label (TPL): Incorporating patient's voice into the TPL allows sponsors' response to the evolving regulatory landscape, and ensures that product labels are more relevant to patients.

Clinical trial design: Patients are experts in living with their conditions and can help sponsors optimise study design and execution to enhance trial participants' experiences, which can lead to improved enrollment and retention

Clinical Outcomes Assessments (COA) Strategy and endpoints selection: A sponsors' COA strategy should be co-created with patients early (e.g., eliciting concepts that are most meaningful to patients, ensure COA tools measure what matter most to patients) to ensure that outcomes and related endpoints incorporated into development are relevant and meaningful to patients.

Dosing experience: Understanding a patient's needs is critical to designing a convenient, easy to use drug delivery system and training experience that will fit into his or her lifestyle.

Benefit/risk management: Direct patient input reflecting patients' willingness to be treated with a product given the risks in exchange for benefits should be consistently incorporated into a product's core benefit-risk assessment, as well as inform the design and evaluation of patient-targeted risk minimization activities.

Regulatory/health technology assessment: Patient input can inform clinical trial design, trial endpoint development and selection, regulatory reviews including benefit-risk assessments, as well as Health Technology Assessments (HTAs) to inform evidence-based health care reimbursement decisions.

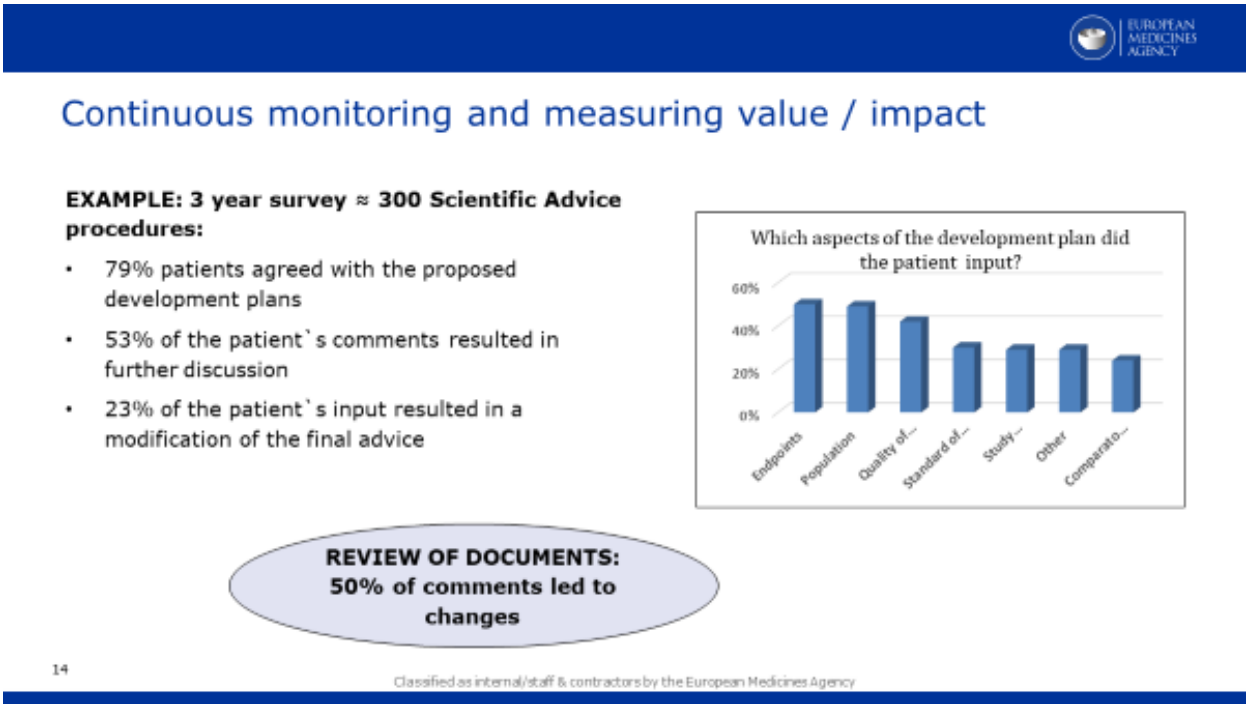
DEEP DIVE INTO EUCOPE RECOMMENDATIONS

Patient Engagement

Patients are already involved in EMA's activities at different levels. A well structure framework for interaction between EMA and patients and consumers and their organisations outlines the basis for involving patients and consumers in Agency activities. [1]

As EMA is continuously acquiring experience from patients' contribution directly to scientific discussions, key aspects are emerging that would define successful engagement. Moreover, continuous monitoring, as recently highlighted by EMA, allows to measure value / impact of such engagement (Figure 2)

Figure 2: Continuous monitoring evolution – extract from 5th EMA R&D platform meeting presentation



To further optimize interactions between patients, EMA, developers and other stakeholders, EUCOPE suggests to:

1. **Revise the EMA framework of interaction to reflect the evolution of patients' contribution to scientific discussions.** The revised framework would provide further clarity and transparency regarding types of engagements and input from patients that have informed regulatory decision. An

[1] https://www.ema.europa.eu/en/partners-networks/patients-consumers#framework-for-interaction-section

example of practical solutions would be the inclusion of a section in the EPAR of how patient experience data informed regulatory decision-making – case examples/case studies

2. We recommend to **actively promote patient engagement throughout drug development** - collection of patient perspectives on various disease areas (not product specific) in the pre-competitive space. This process can ensure that patient perspectives on disease and treatment burden are adequately captured early in development.
    a. Establish two levels of complementary patient engagement:
        i. enhance generation and use of patient experience data
        ii. expand methodologies for patient input during regulatory assessments, e.g. systematic early interactions, focus groups, patient preferences
3. **Structured patient network** - proactive; need to have a representative set of diseases area patients
4. **Exchange methodologies across decision makers** (e.g. HTAs)

Science of Patient Input

To advance the science of patient input and build on the efforts that are already underway, EMA should consider focusing on the following areas:

1. **Development of EMA methodological guidelines**: There is an urgent need for the development and use of approaches, tools and methods to systematically collect, analyze and incorporate patient input into drug development and regulatory decision making across all stages of the lifecycle. EMA will start to see an increase in the patient input (patient experience data) that is submitted in marketing applications, which is either collected by sponsors and other key stakeholders. EMA should provide clear guidelines on methodological approaches and considerations to collecting patient experience data, which will guide Sponsors and key stakeholders to gather robust, fit-for-purpose patient experience data. This will ensure regulatory standards are met and enhance regulatory confidence in the quality and reliability of the study and the patient experience data for its use as evidence in regulatory decision-making. In addition, ICH has also endorsed a reflection paper on patient-focused drug development and outlines plans to develop a series of methodological guidelines. Development of EMA guidelines would aptly position EMA at ICH to strategically shape the new guidelines. Specific topics for guidance development should include the following:
    a. ***Methods to collect patient input throughout drug development:*** This guideline should discuss various methods that could be used when planning to collect patient input, including potential research questions, defining the target population, development of sampling strategy, methods for eliciting information from individuals, best practices in how to do qualitative and quantitative research, conducting interviews, selecting survey questions, identifying when to use various approaches, etc. EMA should also describe how the patient input collected by the outlined methods are considered in regulatory decision-making (e.g., what is the evidentiary standard for the different types of patient input, what is the level of quality and rigor needed for each type of input).

b. Methods to develop, select, or modify clinical outcome assessments and incorporate clinical outcome assessments (COAs) into endpoints for regulatory decision making: This guideline should discuss process for COA development and selection for clinical trials, evaluation of COAs, including development of conceptual framework, generating evidence of context validity, reliability, construct validity and ability to detect change, interpretations of meaningful change; clinical trial design considerations, statistical considerations, etc. The guideline should also discuss considerations for incorporating COAs into endpoints, including determination of endpoint of interest, assessing meaningful within-patient change, use of estimand framework, as appropriate, etc. As appropriate, EMA should consider identifying appropriate timepoints for sponsors to engage with EMA to discuss progress on their development program and obtain early feedback throughout their development program.

c. With the increase in use of COAs in sponsors' drug development programs, there is a need for methodological clarity on approaches to develop and use all types of COAs is critical. Therefore, our recommendation focuses on methodological guideline development for all COAs (PROs, PerfO, ObsRo, ClinRO) and not only PROs. A similar approach has been adopted by other health authorities (e.g., U.S. FDA) and also proposed in the ICH reflection paper on Patient-Focused Drug Development.

d. ***Methodological and regulatory consideration for the use of patient preference information in drug development:*** This guideline should discuss when and how EMA may consider patient preference information, highlight key methods for conducting patient preference studies and preferred qualities of a patient preference study, how to ensure quality and reliability of study data, regulatory considerations and methodological rigor necessary for considering patient preference information for regulatory decision making, and potential gaps and barriers for inclusion of patient preference information.

e. ***Considerations for patient engagement and incorporating patient input into the clinical trial design and conduct***: This guideline should discuss the role of different types of "patients" (e.g., patient advisors, study participants) in informing the design of clinical trials. The guideline should also discuss approaches sponsors may use to engage various types of patients (e.g., Patient Advisory boards) and how the input may inform clinical trial design and conduct (e.g., protocol review, inclusion/exclusion criteria, recruitment/retention strategy).

2. **Enhance EMA-Sponsor dialogue, including EMA's scientific advice**: EMA's scientific advice is currently the main tool for Sponsors to obtain advice on their development programs. EUCOPE sees an opportunity to further enhance the advisory platform, in particular when it comes to discussions regarding patient-focused methods and the collection and incorporation of patient input into drug development program. Below are some proposed enhancements:

   a. ***Strengthen EMA staff capacity to facilitate development and use of patient-focused methods:*** Given the extensive collection and use of patient input and patient-focused methods in drug development, EMA will need to be prepared with the necessary staff expertise and resources to be able to provide constructive advice to Sponsors on their development programs. This could be achieved by establishing a dedicated team composed of EMA's staff with background in psychometrics, statistics, health outcomes research, decision science, etc. With this background, the staff will be able to appropriately advise sponsors and internal review teams on various topics related to patient-focused drug development (e.g., patient input in

clinical trials, COA development and selection, patient preference studies, use of digital health technology, etc.) A key responsibility for the staff would be to /actively contribute to scientific advice meetings to advise sponsors developing new tools or collecting patient/ caregiver input to inform their development program. This team may also peer-review marketing applications when the sponsors have submitted patient input.

b. Establish a new EMA-sponsor dialogue platform and related framework dedicated to the discussion of collection and use of patient input in drug development: To ensure efficient and robust discussions between EMA and sponsors, EMA could consider establishing a new dialogue platform (e.g. using regulatory pilots in a 'sandbox' environment or INNO project) dedicated to provide timely development-phase input/advice to sponsors developing or selecting tools, exploring new approaches or planning to collect patient/ caregiver input to inform their development program. EMA could identify critical timepoints in the development pathway when EMA-sponsor interactions may be most meaningful. An outline of types of data and other information that is most appropriate for each meeting would also be beneficial. This would ensure that Sponsors would be able to appropriately time their interactions depending on where they are in their development program, present appropriate data in the meetings and in the final marketing application, and eventually start a dialogue with EMA early and often.

3. **Establishment of Public-Private Partnership (PPP) and participation in existing PPPs to support global, strategic, and scientific advancement of the incorporation of patient input into drug development and decision-making**: EMA may consider establishing a public private partnership/multi-stakeholder collaborative; and leverage and further support existing PPPs to lead global, strategic, and scientific advancement of the incorporation of patient input into drug development and decision-making. The PPP may consist of representatives from health authorities, industry, patient groups and academia. The PPP could advance work in areas, including:
   a. ***Development of COAs in various therapeutic area:*** PPP could conduct a gap analysis and identify therapeutic areas where there is a need for the qualification of PROs and other COAs. Based on the assessment, working groups may be formed to develop COAs that will be publicly available for use in clinical trials by sponsors where COA-based endpoints are used to support product label claims.
   In addition, EMA should also consider leveraging and supporting efforts such as Critical Path Institute's (C-PATH) PRO consortium that is working with key stakeholders to develop new COAs in select disease areas. Likewise, EMA should consider actively participating in U.S. FDA efforts to develop standard core COAs and related endpoints for the use in decision-making to ensure the core sets are globally acceptable.
   b. ***Advance patient preference methods and studies*****:** PPP could lead efforts to identify and address key barriers and opportunities regarding the use of patient preference studies for drug development and regulatory and HTA decision-making (e.g., how to address biases, framing effects, ensure quality and reliability of study data). Recommendations and considerations may be developed and shared publicly. Case studies may also be developed to share learnings from stakeholders which could inform future EMA guideline development efforts in this area. Any work that the PPP takes on should not be duplicative but complementary to and leverage efforts by IMI PREFER, ISPOR, CIOMS, Patient Focused Medicines Development (PFMD) etc.

c. ***Patient input in HTA decision-making*****:** the level of patient engagement by the different HTAs varies, (e.g. in France HAS, Germany G-BA, UK NICE). We recognize the importance of including patient perspective in HTAs assessment as it ensures that patient input (e.g., patient preferences) are considered in value assessments of new therapeutic options. It is also important that the approach for such patient engagement is aligned with regulators. One existing example is the new Innovative Licensing and Access Pathway (ILAP) in the UK. This pathway has created a single integrated platform for continuous collaborative working between MHRA and NICE, (as well as other partners). The PPP could leverage learnings from ILAP and begin discussions to facilitate the creation of a platform or a pathway would enable early and continuous collaboration between stakeholders would encourage alignment on patient input.

d. ***Advance therapeutic area discussions related to patient-focused drug development*****:** The PPP should also consider convening therapeutic area specific public workshops and closed door meetings to promote discussions and share lessons learned/best practices regarding specific considerations related to patient experience data (e.g., PROs and other COAs--COA development, acceptance of proximal vs. distal concepts, patient preference information, etc.), which is not associated with a specific product/marketing application. This can enhance EMA staff and industry understanding of the challenges, current expectations, and best practices when considering COA, PPI, etc. in their development programs for a given therapeutic area.

Annex I: Overview of Global efforts

U.S: In the US the Food and Drug Administration (FDA) established the Patient-Focused Drug Development (PFDD) initiative in 2012 to collect the patient perspectives on disease and treatment burden by conducting public meetings with patients' stakeholders. In 2017, FDA expanded the efforts to develop a series of guidance documents on methodological considerations for incorporating patient input into drug development and regulatory decision making.

Canada[1]**:** Health Canada is exploring approaches to engage patients, such as by including patient advocates at its standing Scientific and Expert Advisory Committees, as well as through pilots. The Patient Involvement Pilot Project in 2014 was one which explored the value and feasibility of patient input in orphan drugs. This pilot project is also exploring the most effective ways to involve patients in the benefit-risk assessment of therapeutic.

Japan: In 2019, the Pharmaceuticals and Medical Devices Agency (PMDA) established the "Patient Centricity Working Group" to incorporate the patient's voice in both drug and device regulation.

ICH: Recently, in 2020, the ICH Management Committee endorsed a draft ICH reflection paper on proposed ICH guideline work to advance PFDD. In addition, the ICH M4E(R2) CTD overview was updated in 2017, and now includes considerations for incorporating patient perspective into the benefit-risk assessment.

There are also a whole host of activities currently being undertaken across industry association groups, and public-private partnerships such as IMI (e.g. PARADIGM and PREFER), Patient-Focused Medicines Development (PFMD), CIOMS, etc.

References:

1. Klein, A.V., Hardy, S., Lim, R. and Marshall, D.A. (2016). Regulatory Decision Making in Canada—Exploring New Frontiers in Patient Involvement. *Value in Health*, 19(6), pp.730–733.