2022

THE MODERNISATION OF THE CENTRALISED PROCEDURE

A PROPOSAL FOR REFORM

A Position Paper prepared by the EUCOPE Regulatory Working Group

EUCOPE
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19 April 2022

EUCOPE'S POSITION ON THE REFORM OF THE CENTRALISED PROCEDURE

Context

As part of the ongoing review of the General Pharmaceutical Legislation[1] and the implementation of the Clinical Trials Regulation, we intend to outline our vision for the evolution of the EU Regulatory framework and a modernisation of the Centralised Procedure with regards to less complexity, more agility and more predictability to ultimately bring innovations earlier to patients. This document and its position are based on the EUCOPE regulatory strategic workshop, held on 29 November 2021, with 34 experts from 22 EUCOPE member companies, including 9 small and mid-sized companies, across Regulatory Affairs, Intelligence, Policy and Market Access.

Position Paper

Executive Summary

EUCOPE proposes a more streamlined approach to the European Centralised Procedure (CP) for marketing authorisation of innovative medicines in the EU along the value chain:

I. EUCOPE proposes to update and streamline the eligibility criteria and assessment based on most current needs and health care challenges by focusing the scope on complexity of the products while remaining flexible to capture different levels of innovation.

II. Committed to maintaining the highest quality, safety, and efficacy review standards, EUCOPE proposes reducing the time to the EMA's opinion on the marketing authorisation (MA), maintaining a thorough scientific evaluation.

III. EUCOPE proposes a re-think of the European Commission's (EC) decision on MA, decouple the decision making and the translation of the patient information (PI) in all EU languages and consider which procedures could finish at the level of the EMA, that would not necessitate a Commission decision.

[1] Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use (OJ L 311, 28.11.2001, p. 67) and Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency (OJ L 136, 30.4.2004, p. 1)

Introduction

The European Centralised Procedure (CP) has helped and accelerated the approval of novel medicines across EU Member States since its first introduction in 1995. While updates have occurred over the past 25 years, the revision of the General Pharmaceutical Legislation, as part of the Pharmaceutical Strategy for Europe[2], presents an opportunity to modernise the procedure and ensure it is fit for purpose and future-proofed for innovative therapies.

A regulatory approval process that is well equipped to assess novel and increasingly complex medicines is critical to accelerate patient access to innovative treatments in the EU and beyond. While the European Medicines Regulatory Network (EMRN) and the CP are unique and examples of regulatory best practice globally, these need to further progress to keep pace with current and future innovation. Understanding the human and financial resources constraints of the EMRN, we want to put forward EUCOPE's proposal for the evolution of the Regulatory framework over the next decade. Our proposals take into account the goals of the European Regulatory Network Strategy and the EMA's Regulatory Science Strategy to 2025.

Therefore, in order to modernise the procedure, EUCOPE calls for improvements along the value chain, accompanied by updated scope of the CP, simplification of its complex operations, streamlined timelines and increased global competitiveness.

These improvements can be achieved by making substantial changes at three steps of the MA's process: **pre-submission, evaluation, and decision-making**. In addition to helping accelerate the speed at which patients can access potentially life-saving and transformative therapies, these reforms can help make the EU a more competitive region for investment in the R&D pharmaceutical sector.

PRE-SUBMISSION

The pre-submission phase includes several steps prior to submitting an application to achieve a marketing authorization via the centralized procedure in the EU. It includes eligibility assessment, notification of intent, pre-submission meetings and can take as long as 18 months.

[2] Communication on a Pharmaceutical Strategy for Europe, 25 Nov 2020
[3] CIRS R&D BRIEFING 81: New drug approvals in six major authorities 2011-2020
[4] EMA annual Report at https://www.ema.europa.eu/en/documents/annual-report/2020-annual-report-european-medicines-agency_en.pdf

During the current pre-submission phase, elements can be modernized to reflect the technological developments of the intervening decades, ensuring that resources are allocated where needed most and to streamline the following approval process. EUCOPE sees two main challenges with regards to the current pre-submission process:

Challenges:

The eligibility criteria for the centralized procedure have been the same since the introduction of the EU procedure described in the Reg 726/2004 as amended and could benefit from reflection on current innovation and healthcare challenges.

The pre-submission phase is mostly focused on administrative issues, lacking alignment between the development stages and review stages of therapeutic candidate. Rather than creating administrative burden between these two phases and prolonging the process, it is important to streamline and integrate the two phases to allow for the swift, appropriate and timely assessment of therapies.

Why is it an issue:

The resources for eligibility request and assessment are needed for processes that bring value.

Due to the long pre-submission time, the actual submission is prolonged and ultimately early patient access hindered. The operational and administrative focus of the pre-submission stage takes focus away from strategic discussions, evaluation timelines, communication, and procedures. In addition, the misalignment between development stages and review stages hinders a streamlined process to speed up the approval process. Resources at the EMA and developers are limited likewise and could be used where needed more to really support innovation.

Recommendation for proposed solution:

General statement on improving CP eligibility:

- EUCOPE proposes to update the CP eligibility based on most current needs and health care challenges by reviewing the scope and assessing whether some are still applicable. We propose to focus the scope on complexity of the products while remaining flexible to capture different levels of innovation.

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[3] CIRS R&D BRIEFING 81: New drug approvals in six major authorities 2011-2020
[4] EMA annual Report at https://www.ema.europa.eu/en/documents/annual-report/2020-annual-report-european-medicines-agency_en.pdf

- EUCOPE proposes to streamline the eligibility assessment by simple registration for products in mandatory scope and assessment only if doubts exist in the intent from sponsors, possibly anticipating it to development/advice interactions.

- EUCOPE proposes to reduce the 18-month prior to MAA eligibility timeline and streamline based on available information from development advice, which can be facilitated by electronic means, e.g. IRIS.

Bridge the development and evaluation gap

- EUCOPE appreciates the link to workforce-planning / horizon-scanning based on other means (e.g. business pipeline) to anticipate information needs on eligibility and pre-submission.

- EUCOPE proposes to move to a central contact person lead at the EMA that helps "shepherd" the asset throughout the development into evaluation, ensuring dialogue throughout and avoiding conflicts of interest (e.g. related to Ombudsman recommendations).

- EUCOPE proposes to strengthen continuum of the dialogue and consider milestone meetings to increase familiarity with the file ahead of pre-submission. Alternative pre-submission stage interactions (e.g. ITF, SA, business pipeline meetings) could be strengthened in order to be used in the actual assessment phase. This would ultimately ensure a continuity between Scientific Advice Working Party Rapporteurs and the Rapporteurs for the assessment of a Marketing Authorisation Application.

Set the stage for a seamless review flow

- EUCOPE proposes to leverage the pre-submission stage to turn the focus from the CP process to content matters, helping increase predictability and align on gaps prior to the start of the procedure, aligned with advice received during development.

- EUCOPE proposes to reduce any further administrative burden on the pre-submission step (e.g. leverage platforms like IRIS)

- EUCOPE proposes to keep the pre-submission interactions flexibility rather than keep it a mandatory step.

- EUCOPE proposes to focus on joint content and procedure-focused pre-submission meeting. This could be managed by the EMA primarily as an application orientation meeting.

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Regulatory and Stakeholders' roles and responsibilities

- EUCOPE asks for a clear focus during pre-submission interactions on regulatory stakeholders and extend to possibly others of interest in certain product types (e.g. notified bodies in combination products)

- EUCOPE asks to ensure Cross-Committee pre-submission interactions, which could be facilitated by Multi National Authorisation Teams (MNATs) formation via the central contact point (see section II below)

- EUCOPE proposes a better alignment between different Committees in order to gain more predictability based on how different Committees see the holistic development package (e.g. how pediatric plan impacts compliance check for the adult MAA)

- EUCOPE suggests to reinforce and expand the involvement of patients in EMA activities and their input being appropriately weighted in regulatory decision making. EUCOPE proposes to systematically embed the voice and experiences of patients in the clinical assessment of outcomes.

EVALUATION

Challenges:

- The EU boasts an internationally renowned regulatory evaluation process, with a structured procedure and clearly defined timelines. Yet, when compared to other world regions or countries, the EU has one of the slowest median approval times for novel therapies[3]. In part, this stems from the fact that the Centralised Procedure is complex, lacks agility, and includes some inefficiency and administrative burden. Even for the EMA's early development accelerated regulatory pathways, e.g. PRIME, the envisioned acceleration is not comparable with other regions[3].
- Duplication of effort is inherent in the current evaluation process. Added to this, there is an uneven distribution of expertise and Rapporteurship across Member States [add figures from EMA Annual Report]. Both of these factors contribute to the lack of suitable resources available when needed. The current regulatory framework has not met expectations in an even distribution of qualified expert EU Assessors from across the EU Member States and is not fit for purpose in supporting the development of future generations required to effectively meet the increasing demand and expectations.

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[3] CIRS R&D BRIEFING 81: New drug approvals in six major authorities 2011-2020
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Why is it an issue:

- The complexity, challenges and lengthy timelines for evaluation ultimately leads to EU patients having access to innovations and important treatments later than in other regions[3].
- The current binary approach of Rapporteur and Co-Rapporteur Assessment Teams, with its duplicative efforts and potential for different approaches, is resulting in compilation of long lists of unrelated, repetitive questions that lack prioritisation. This, in turn, is resulting in burdensome and resource-intensive efforts by Applicants in responding to those questions, contributing to long clock-stop times, lengthening the overall evaluation timeline.
- The complex and slow procedure undermines the EU's global competitiveness and companies may decide to delay EU filings in favour of other regions.

Recommendation for proposed solution:

Committed to maintaining the highest quality, safety, and efficacy standards, EUCOPE proposes reducing the time to the European Commission issuing Marketing Authorisations. This can be achieved through reviewing and streamlining the EMA evaluation process, reducing the long list of unstructured questions towards a common understanding of prioritisation, which would result in shorter clock-stop periods, whilst maintaining a thorough and extensive review.

Our vision is that the EU regulatory framework empowers **a collaborative European assessment for the CP, with a system for assessment based on rigorous scientific process and methods**.

After 30 years, the EMRN has learnt to work together and there is a mutual trust amongst CHMP members – this proposal aims to leverage those achievements, and rather than the current binary system, aims to build consensus from the beginning of the evaluation.

Another objective is to enable the ERMN to grow more in expertise, empowering national agencies that have less resources/ expertise to access a European training platform.

This could be achieved through three interconnected proposals:

1. Supporting an European MAA scientific evaluation: Appointment of Rapporteurs with greater transparency, Applicant input and expertise development.

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[3] CIRS R&D BRIEFING 81: New drug approvals in six major authorities 2011-2020
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- EUCOPE believes, that mandatory training, support, and information sharing, should be in place to encourage development of Rapporteurs from all EU MSs. This could avoid the same Rapporteurs being assigned too often with lack of development of expertise in other MSs and would also help develop consistency. An *EU Regulators' Academy* for medicinal products assessors, run by EMA, could support an EU curriculum including hand-on experience on CP. Successful completion of the curriculum could be a mandatory requirement to be part of assessment teams. A common curriculum will also promote consistency of assessment and keep assessors abreast of innovative regulatory science approaches.
- Performance of assessment teams should be measured with transparent KPIs (e.g. speed, accuracy of assessment, number and type of questions, clarity of communication and engagement, coordination). The performance evaluation should take into account feedback from peers and from applicants.
- EUCOPE identified the need to improve the nomination of Rapporteurs. We propose that EMA takes into account Applicants' preference in form of a list of 3-4 Rapporteurs based on performance of assessment teams. This could ensure appropriate expertise and consistency (for example with previous submissions, experience in Member State (MS) with clinical trials), to shorted review times and reduce questions allowing faster responses and resolution.
- A Therapeutic Area model for bringing together relevant expertise is another model which could create transparency in appointment of assessors and consistency in their assessment. Note, an Agency may not be proposed solely based on TA expertise, other aspects would also be considered, such as experience with a particular procedure. A process could be considered for the situation where the Applicant does not agree with the views/ assessments of the established expert/ expertise centre.

2. Embracing Multinational Assessment Team (MNAT) configuration: reinforce appointment of best available assessment team while avoiding duplication of assessment, with one expert assessment team bringing together relevant expertise.

- One assessment team (i.e. no separate Rapporteur and Co-Rapporteur teams) could shorten timelines to Assessment Report (e.g. D80 reduced to D60). No Joint Assessment Report would be required, therefore, the List of Outstanding Issues could be provided earlier (e.g. D180 reduced to D150). Multi-national/ discipline teams, could mitigate the need for a Co-Rapporteur and make this more acceptable.
- Lack of Co-Rapporteur would mean only one key opinion and may be challenging in the case of disagreement between the Applicant and the Rapporteur. An additional potential challenge is that little engagement is often seen from the other experts included in multi-national teams. Appropriate selection of Rapp will be key to overcome these challenges (and is covered in part in the proposal above).

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Consideration should be given on how to promote engagement from other experts included in multi-national teams and consider enhancing the EMA peer-review role.

- Currently timelines are linked to CHMP meetings, which adds in another time constraint that can lead to delays in evaluation and opinion. Consideration should be given to reduce delays due to link to CHMP meetings by getting endorsement outside of the monthly CHMP meeting. We propose that CHMP opinion should be reached via written procedure, unless exception due to complexity or unclear evaluations with specific issues to be addressed that require discussion at that forum. This also impacts other committees e.g. PRAC, PDCO etc.

3. Staggered submission of dossier/ dynamic assessment

- Submission of the dossier could be staggered so that modules are submitted by the Applicant as completed rather than in one batch, to allow for ongoing review and feedback of questions. Questions could then be received in batches based on themes and interlinked topics, for example pre-clinical/CMC could come in batches.
- Initial submission: There is potential for modules 3 & 4 to be submitted earlier. Response to questions: Receiving batches of questions would mean that the Applicant can work on a smaller set of questions at any given time, which could help with resource. Questions could be received by the Applicant from D30, with a maximum of Day 60 for the full list of draft questions.
- Current timelines are predictable, which has significant benefit in terms of planning workload and resources and certain set predictable timelines should be maintained within these new proposals, for example by having a range of days and maintaining a maximum timeline for staggered submission and review. There is overlap across areas, therefore, waiting until an entire module is complete before submission would be the best approach e.g. all clinical questions received at once.
- Multiple day 1 for each batch of submission could lead to complicated and overlapping timelines for the rest of the procedure, therefore consideration and agreement on how batches would be grouped is needed. A proposal could be developed for batching questions appropriately and timelines to avoid duplication and re-work e.g. pre-clinical, clinical, CMC.

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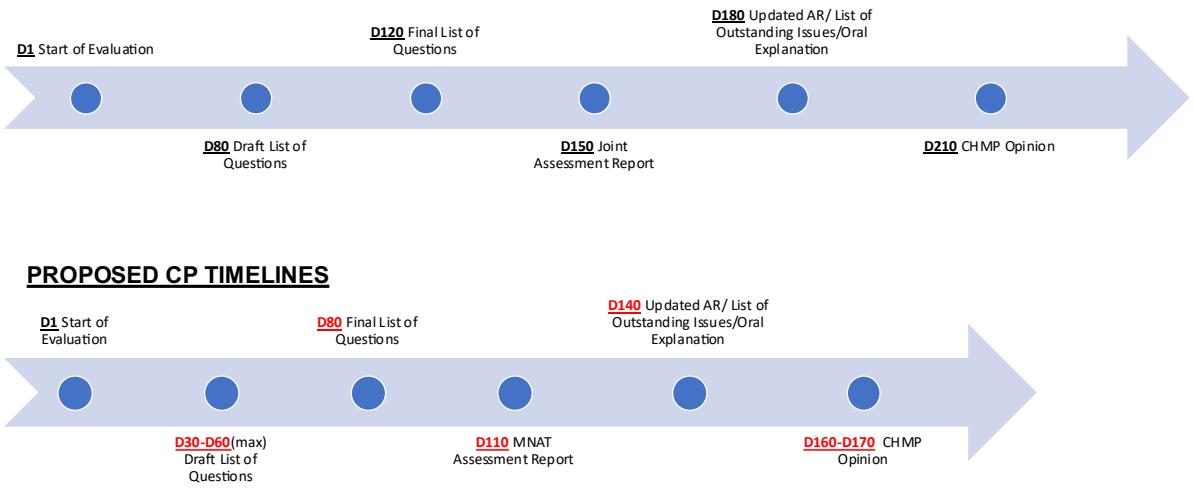
Proposed impact to timelines:



- Draft list of questions – Day 30-60 (current Day 80): Questions could be received by the Applicant from D30, with a maximum of Day 60 for the full list of draft questions. Reduced as have opportunity to send questions in advance – helps with management. Use of MNAT teams to distribute resource.
- Final List of Questions – Day 80 (current Day 120): Reduced as address clarifications earlier and ongoing. Alternative ways to ratify questions via written procedure e.g. emails, not at monthly CHMP meeting.
- Multinational Assessment Report – Day 110 (current Joint Assessment Report Day 150): Propose to maintain 30 days for review of Applicant's response to allow sufficient time and ensure thorough review and completion of AR.
- Updated AR, List of Outstanding Issues/ Oral Explanation – Day 140 (current Day 180). CHMP Opinion reached via written procedure, unless exception.
- CHMP scientific opinion – Day 160 – Day 170 (current Day 210) - Range depending on list of outstanding questions. Normally D160 would be expected target, with Day 170 for more complex issues to resolve.
- Overall timeline reduction 40-50 days.

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Feasibility of the proposed reduction of assessment time:

Considering the statistics of the assessment time on average being 190 days[4], a reduction of the legally provisioned 210 days has already been demonstrated in the current system. Implementing our practical solutions, therefore the proposed timeline of 170 days seems achievable.

For some products we can even envision shorter assessment timelines, where preconditions can be demonstrated, such as a well-planned R&D program, a solid and convincing data set, limited number of expected questions and a commitment of short clock stop periods.

DECISION-MAKING

Challenges:

- Regulatory decision making by the CHMP resulting in a published opinion is the final step before approval by the EC in the EU.
- The granting of a marketing authorisation by the European Commission as the official legal body in the EU is the final and a separate step following scientific benefit-risk assessment by the CHMP. Translation into all official EU languages is included in this step. The timeframe given for this legally defined approval is 67 days for new MAAs, up to 2 months for variations. Although the EC was able to fast track decisions in the context of the pandemic approval to a minimum of 2 days, the average time is around 50 days[4].

Why is it an issue:

The timeframe of 67 days for the EC decision is a long and protected legal process with little added benefit. Any day following CHMP scientific opinion leads to delayed market access discussions and ultimately patients' access.

Recommendation for proposed solution:

- EUCOPE proposes a re-consideration of the current legally defined decision-making timelines, resulting in faster decision-making processes. In addition, we propose that the decision making and the translation of the PI in all EU languages is decoupled; the decision would be issued on the basis of the

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EN version of the Product information. The translations to all languages could be run in parallel, but be distinct to the decision making, which would help progress the decision more swiftly.

- EUCOPE proposes to consider which procedures could finish at the level of the EMA, not necessitating a commission decision.

Conclusion

Summary of key recommendations

EUCOPE recommends to establish a more streamlined approach to the European Centralised Procedure (CP) for marketing authorisation of innovative medicines in the EU along the value chain. EUCOPE proposes three core recommendations:

1. update and streamline the **eligibility criteria and assessment** based on most current needs and health care challenges by focusing the scope on complexity of the products while remaining flexible to capture different levels of innovation.
2. reduce the **standard timeline for EMA assessment to 170 days** by streamlining the process through introduction of collaborative trained and qualified Multi National Assessment Teams thus resulting in shorter evaluation and clock-stock times, whilst maintaining a thorough and scientific review.
3. re-consider the **requirement for a European Commission's decision step**, and decouple the decision making and the translation of the patient information in all EU languages.

EUCOPE's proposals to reform the Centralized Procedure aim to develop a more future system that responds to needs of developers and patients. The proposed streamlined regulatory approval process is designed to assess novel and increasingly complex medicines more efficiently, accelerating patient access to innovative treatments in the EU and beyond.

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