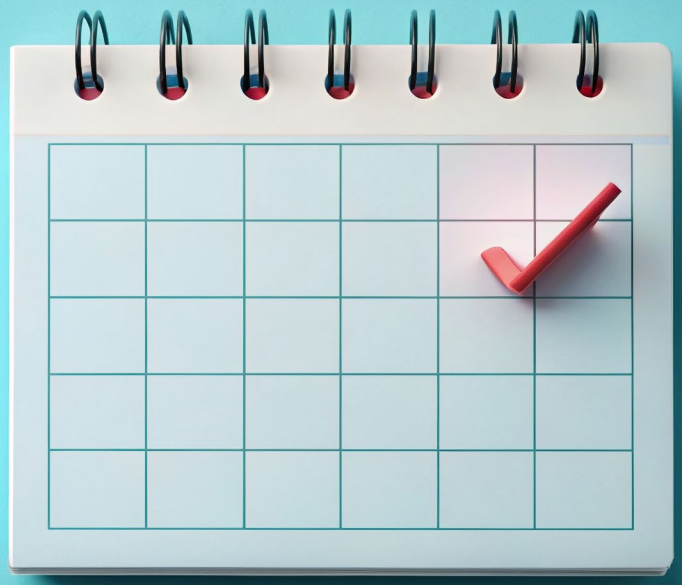
HMA
Heads of Medicines Agencies

EMA
EUROPEAN MEDICINES AGENCY

Joint HMA/EMA multi-stakeholder workshop report on submission predictability

Workshop report

25 September 2024



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1. Contents

2. Introduction and motivation

This multi-stakeholder workshop was organised to discuss ways to enhance submission predictability and to raise awareness of the implication and challenges that frequent and multiple delays to the submission dates pose on the Network's resources and planning.

The workshop aimed to bring together representatives from the national competent authorities (NCAs), industry, and EMA, to foster a common understanding of the problem and to highlight case studies from all parties, each facing different challenges.

The event showcased the problem statement and was followed by a best practice approach for submitting a Marketing Authorisation Application under the centralised procedure. Case studies from both NCAs and industry were presented, followed by a Q&A session and a panel discussion where best practices were shared. The recurring message from all parties was the need for better and more frequent communication.

3. Sessions

3.1. EMA statistics on submission predictability and problem statement

Unreliable long-term planning for initial marketing authorisation applications (MAAs) for centralised procedures has been a recurrent problem for the network for many years but it has become unsustainable with resources stressed to the limit due to Brexit and subsequently by the COVID-19 pandemic. To quantify the problem, we have analysed the trend of the past years and observed that less than half of the applicants submit an MAA as initially communicated with the letter of intent. Most MAAs are delayed or even withdrawn resulting in a considerable disruption of the regulators' workplan. This prompted us to take action and in June 2022 it was decided to create a focus group to perform a root cause analysis of the reasons for such delays and to propose solutions to improve the trend. The focus group on submission predictability, formed by regulators and industry representatives, started work in November 2022. The deep analysis of the year 2023 confirmed the poor behaviour observed for many years and highlighted objective insights to improve predictability.

3.2. Best Practice approach using current guidance

Eligibility to the centralised procedure has to be confirmed in advance of submission of application. Applicants are advised to request it by submitting the pre-submission request form (Eligibility) with its Annexes between 18 months and 7 months prior to the planned MAA submission date. Following confirmation of eligibility to the centralised procedure a Product Lead (PL) is appointed. The PL is the primary contact point of the applicant with EMA in relation to the upcoming MAA.

Appointment of rapporteurs is triggered by submitting the "Letter of intent" (LoI) together with its Annex. The LoI should be submitted 7 months prior the intended submission date. This LoI should include a realistic and accurate date for submission. With this request, the applicant is informing EMA about their intent to submit the MAA using a specific slot and requesting EMA and the national agencies to commit resources to the assessment of the dossier.

Three months before intended submission date EMA will seek confirmation on the submission of the MAA by the specified date in the LoI. It is critical that applicants respond to this confirmation e-mail. In any case, if it becomes apparent that the initially indicated submission date for an MAA will not be met, this should be communicated as soon as possible, including the reasons for the delay and an alternative submission date (based on realistic timings).

Applicants are strongly encouraged to engage in early dialogue with EMA/Rapporteurs during pre-submission phase. The pre-submission interaction with EMA and Rapporteurs is meant to provide responses to scientific/regulatory/procedural related questions and assist companies in the finalisation of their upcoming MAA, in order to ensure the validation of the MAA is satisfactory, and the dossier is mature. No substantial data derived from new studies should be introduced as part of the responses to the List of Questions (LoQs) or List of Outstanding issues (LoOIs) that were not specifically requested by EMA's human medicines Committee, the CHMP.

The LoQ at day 120 should be responded within 3 months and the LoOI should be responded to within 1 month. Applicants may request an additional period of up to 3-month at day 120 and 1-month for providing their responses. The request should be duly justified by using the existing form and it will be reviewed and agreed by the CHMP. The CHMP is applying the strict principles

on clock-stop as outlined in the CHMP guidance from 2009[1]. Hence, when preparing the MAA, applicants should plan to have a maximum of a 3-month clock-stop at day 120- and a 1-month clock-stop at day 180. Applicants should avoid the submission of an initial MAA with interim data knowing it may not be sufficient to reach a positive opinion, with the expectation to complement with full data following prolonged clock-stops.

If an intended submission date is not met, a discussion should be initiated with EMA to assure the availability of assessment teams and explore the need for an adjustment of the submission date if warranted.

3.3. Views & concerns from Member States on Submission Predictability

3.3.1. Consequences of poor submission predictability:

- Each case of delay or withdrawal has an impact on the resources of all assigned rapporteurs
- Strained resources in the network, increasingly difficult to assign rapporteurs for all applications – which has an impact also on other procedures (e.g. lifecycle, MRP/DCP)
- The use of multinational assessment teams helps in some cases, but increases the complexity even further
- The assigned rapporteur may need to step down, sometimes at a late stage
- Inefficiency of the system increases costs

3.3.2. Ideas for improvement:

- More mature applications
- Realistic submission dates in the letter of intent (LoI)
- Early communication about arising submission delays
- Proactive discussion(s) with Rapporteur teams and EMA
- Improved clock-stop predictability
- Improved predictability (communication) of type II variation and extensions submissions

3.4. Update on Rapporteur appointments

The Agency provided an overview of the process of appointment of CHMP Rapporteurs for (MAAs) in the centralised procedure that takes place 6-7 months before the intended submission date.

Over the last 4 years, the delays in submission of MAAs have led to changes in rapporteurships in 5-8% of MAAs. Full replacement of rapporteur has been associated with longer submission delays while changes of a rapporteurship of one single MS into a multi-national assessment team (MNAT) are linked with shorter delays.

[1] Time allowed for applicants to respond to questions and issues raised during the assessment of new marketing authorisation applications in the centralised procedure | European Medicines Agency (EMA)

EMA is closely monitoring the impact of delays and may consider additional measures if the rate of changes in rapporteurship due to delays increases.

The Agency also presented the provisions of the new regulation governing the fees payable to EMA for pre-submission activities and changes in submission dates for MAA that will be applicable from 1 January 2025. A fee is due for each change in submission date beyond 60 days from the date declared in the initial letter of intent, even if justified and agreed with the rapporteurs during pre-submission interactions.

3.5. Industry representatives' viewpoints on submission predictability

The pharmaceutical industry is committed to enhancing submission predictability and fostering better communication with EMA and rapporteurs. This commitment includes defining the intended submission dates with care and adhering to the EMA/HMA Best Practice Guide and EMA pre-authorisation guidance. We recognise that the lack of predictability in submissions impacts EU Network resources and ultimately patients access to medicines.

The primary goal of the industry is to reach all patients that can benefit from the medicine to have access to it (by launching medicines globally as early as possible) and companies routinely employ global development and registration strategies. This includes a critical role for the EMA as some global Regulators rely on EU's regulatory authorisation decisions. Global filing plans are drawn up taking into consideration commercial and access perspectives and will always be underpinned by a business case, which is negatively impacted by changes in submission dates.

While the industry strives for improved predictability in submission dates, achieving 100% success is not realistic (in the context of timings of the Letter of Intent and annex) since there are several factors that can contribute to changes in submission dates for innovative medicines including:

a) **Uncertainty of Clinical Trials Outcomes:** Trials may fail or require extensions, impacting timelines.

b) **Regulatory Environment Complexity:** Navigating global regulatory landscapes can introduce unforeseen challenges.

c) **Multi-regional Clinical Trials:** The complexity of global submissions can affect timelines.

d) **Patient Recruitment Duration:** Uncertainty, especially in rare diseases, can lead to delays.

e) **Revised Statistical Analysis Plans:** Additional or revised plans may be necessary after expert input.

f) **Last minute Regulator Requests:** Additional studies may be requested during pre-submission interactions.

g) **GMP and GCP Issues:** Data integrity concerns can arise unexpectedly.

h) **Business factors:** Mergers, acquisitions, and resource allocation can influence timelines.

i) **Time to Event Based Endpoints:** Variability in expected timelines can cause adjustments.

j) **Third-Party Issues:** Challenges related to the manufacture of active substances, excipients, reagents or external contractors/consultants can also impact submissions.

k) **Lack of knowledge of European Regulatory framework:** Lack of experience in submitting in Europe and/or a need to use consultants.

The industry presentation highlighted that changes in submission dates are in line with submissions to other global regulatory authorities. Industry sees on average that innovative medicines file in Europe less than a month after the US[2].

The industry aims to maintain the EU's leading position, to ensure medicines are provided to patients as early as possible and is committed to enhancing submission predictability which is a priority topic on trade associations' agendas. Establishing earlier dialogue with regulators is considered a vital step, as increased interactions can substantially improve the likelihood of timely submissions. However, the industry recognizes that positive clinical trial outcomes are essential for ensuring complete dossiers and timely submissions. Effective communication is acknowledged as a critical factor in achieving these objectives.

3.6. Case studies: Innovators, Generics and Biosimilars

3.6.1. Case Study 1

This first example from an innovator's company illustrates a case study involving an innovative oncology product for breast cancer, characterized by a complex drug development plan. The event-driven study design affected the anticipated submission timing, necessitating additional flexibility in the submission timelines. Furthermore, strategic changes were made regarding which studies to include in the submission, requiring further interactions with the EMA and Rapporteurs. Such flexibility is required to ultimately provide new medicines to patients as early as possible.

The key takeaways from this case are that proactive and transparent communication with the EMA and Rapporteurs' teams are essential for planning adjustments to timelines and submission dates. Additionally, it was emphasized that European approvals hold significant international importance, as many countries rely on EU authorisation decisions. Thus, achieving optimal and early EU submissions and approvals will have a positive global impact.

3.6.2. Case study 2

This second example from an innovator's company illustrates a case study for first-in-class product intended to treat a disease with high unmet need whose MAA submission date had to be postponed 3 times.

The regulatory filing strategy included global filings in major markets, including the US New Drug Application (NDA) and EU MAA and clinical data package contained a Phase 2 single arm trial (SAT) for indication A and a Phase 3 study for indication B with pre-specified interim and final analyses. During agency interactions, the FDA concluded that filing based on SAT would be acceptable for NDA approval in indication A, leading to the company's decision to file with results from SAT in the US. However, the CHMP concluded that filing based only on SAT was not

[2] CIRS RD Briefing 93 – New drug approvals by six major authorities 2014-2023, available online at https://www.cirsci.org/publications/cirs-rd-briefing-93-new-drug-approvals-by-six-major-authorities-2014-2023/, Retrieved on 10 August 2024.

supported and desired a randomized clinical trial to support the MAA in indication A. Consequently, the company decided to combine indications A and B in the EU.

Pre-submission interactions with EMA resulted in 3 delays due to various reasons including delay in the availability of the Phase 3 study results at next event-driven interim analysis with more mature data, more time needed to build the MAA dossier and author CTD modules (vs supplemental NDA for US submission) and internal discussions in a very select group of unblinded people.

This example highlighted the complexities and challenges faced by the innovator during pre-submission interactions with EMA which impacted the submission predictability.

3.6.3. Case study 3

In the third case study, Industry initially highlighted additional representative examples that can **trigger changes in submission dates or withdrawals of planned applications:**

- **Pivotal study fails** - A failure in a pre-planned interim analysis can lead to significant delays with an impact on planned timelines or even withdrawal of a planned submission.
- **Pivotal study results not clear-cut** - If the results are not clear-cut, the sponsor may require additional time for further analysis, re-evaluation of the statistical plan, and adjustments to the submission strategy. This necessitates more interactions with health authorities, including Rapporteurs' teams, which can impact planned submission timelines.
- **Data integrity issues** – various scenarios (Internal audit/whistle-blower generates concern with dossier data after Letter of Intent issued, cyberattack – data requires review for validation purposes) can trigger delays in submission to allow company to investigate.
- **EMA submission follows first-global approval** - Dossiers developed initially for a single regulator (no global strategy in development) are unlikely to meet EMA requirements without changes e.g. additional studies, re-formatting, translations which may be challenging to predict ahead of pre-submission interactions, especially for companies unused to filing in Europe.

A summary of the relevant EMA guidance to improve submission predictability was shared, with a focus on the top 5 Best Communication Practices to be implemented by industry to support health authority planning when changes in planned submission dates do occur. This included recommendations on the process to follow when a change in submission date is identified by a company after a Letter of Intent has been submitted. A specific industry case study provided an example of best practices to follow where:

- The need to change the planned submission date was communicated as soon as identified (ahead of rapporteur appointment)
- The new planned submission date was feasible and realistic, and reconfirmed with EMA at the 3-month automated reminder

3.6.4. Case study 4 – Generics and Biosimilars

Generics and biosimilars cannot be submitted until the reference product's regulatory data exclusivity has expired, and they cannot be launched until both regulatory marketing protection and intellectual property protection have expired. Submission dates are set by counting

backwards from the planned launch date to allow time for regulatory approval and launch preparation activities whilst respecting data exclusivity afforded to the reference product. Launching generics and biosimilars as early as possible (ideally on day one) is important to ensure early availability of more affordable medicines to patients and healthcare services and to recoup development costs for future investment.

Development cannot start immediately on approval and launch of the reference product. To best serve the needs of patients in the long term it is necessary to operate a sustainable business. This means that companies need to be selective in terms of which products they chose to develop taking into account potential market size, future market changes, scope for partnerships with other companies and overall appetite for risk (as some products are more difficult to develop than others). This process takes time and development start dates are often a delicate balance between ensuring that there is a robust business case and allowing sufficient time to complete the development.

Once a business case has been established several factors can influence development start dates such as waiting for the active pharmaceutical ingredient to be available. Although contingency is usually built in to accommodate potential delays in the development process, timelines can often be quite tight. Issues with steps at the end of developments such as unforeseen challenges during manufacture of submission batches or delays in starting/concluding a bioequivalence study can lead to a need to change an agreed submission date, particularly if these steps take place in the final months before submission. Where unforeseen issues impact on an agreed submission it is important however that these are promptly and transparently communicated to EMA.

4. Recommendations for industry

To improve submission predictability, the below recommendations for industry are crucial and must be considered when preparing a Marketing Authorisation Application. It is important to remember that when submitting a Letter of Intent, the applicant is requesting the national agencies and EMA to commit resources to the assessment of the dossier.

4.1. Key messages

Enhance communication

- Early and closer dialogue with rapporteurs and EMA via pre-submission interactions or meetings to ensure the dossier is ready and complete in time for the intended submission date.
- Inform immediately the rapporteurs and EMA when an intended submission date is no longer feasible and provide a detailed and robust justification for the delay.
- Contact the rapporteurs to discuss and agree on the new submission date to make sure the date is realistic and accurate. In case of lengthy delays, the rapporteurs and respective assessment teams can no longer be guaranteed.
- Reply promptly to EMA's automated reminders to confirm that the intended submission date is still valid.
- Promptly notify the Rapporteurs and EMA when circumstances change.
- Ensure EMA and Rapporteurs have an updated and reachable point of contact responsible for the application.
- Communicate planned post-authorisation submissions (e.g., line extensions, extension of indication and major Type II variations) in response to the automatic email notification which is sent to all marketing authorisation holders on 1 May and 1 November each year.

Maturity of dossier

- Thoroughly consult EMA guidelines before submitting an application: Scientific guidelines
- Be realistic about the intended submission date and base it on the availability of the supporting data.
- Do not plan for long clock-stops during the evaluation – CHMP is implementing its 2009 guideline strictly and will generally not allow long clock-stops. All requests for clock-stop extension need to be well justified, and approval is at the discretion of the CHMP/CAT. Clock-stops requested due to an immature application dossiers will no longer be granted.
- No substantial data derived from new studies should be introduced, unless requested by the CHMP, during the evaluation.

Submission readiness

- Ensure the submission file is ready for validation and compliant with the legal and regulatory requirements by using the validation check list and EMA pre-authorisation guidance in preparation of submission

Regulatory and administrative content validation checklist:
https://www.ema.europa.eu/en/documents/template-form/dossier-administrative-validation-checklist-initial-marketing-authorisation-applications-applicants_en.zip

Pre-authorisation guidance
Submission dates

5. Responses to Slido questions

No.	Question proposed	Response
1.	Hello, will you be able to share all presentations with participants after the workshop? Thanks a lot!	Yes, they will all be published on the EMA website: Joint HMA/EMA multi-stakeholder workshop on submission predictability
2.	Could you also share some clarity into how much time does it takes to find coordinators for scientific advice? Thank you	The Scientific Advice Coordinator nomination takes almost 4 weeks including 3 rounds of bidding and assignment. Depending on the number of procedures, the majority of coordinators will be assigned by the end of the 2nd week (end of 1st round) with fewer and fewer coordinators assigned in round 2 and 3, respectively.
3.	What are the plans to lifecycle management? Are similar requirements foreseen post approval?	Currently we do not request Letters of Intent for post-approval submissions, with the exception of Line Extensions. Since May, this year (2024) we have implemented an automatic email notification which is sent directly to all contact points for all marketing authorisation holders on 1st May and 1st of November. In this email, we request a list of all planned post-approval submissions (the major ones) to be sent directly to the Rapporteur teams. This will give us a bit more visibility of the workload related to the lifecycle of products.
4.	Do you have KPI linking delays in filling and delays within the procedure (delays in availability of pAR and AR)?	We do keep KPIs on the availability of the preliminary and updated assessment reports from the Rapporteurs. In general, Rapporteur teams are good at delivering these reports on time, although of course there are individual exceptions. We have not looked at whether there is a correlation between the date of submission being moved and a late delivery of assessment reports. It would be interesting to see if indeed there are never any delays for submissions that are made on time.
5.	If a clock stop extension is refused, does that mean that the MA application will be refused, or the applicant will have to withdraw their application?	No, if a clock-stop extension is refused, the applicant will be expected to submit responses by the date determined by the CHMP. If no responses are submitted, the procedure will continue per its normal timetable, the Rapporteurs will update their report, and since not all issues will have been resolved, a negative opinion will be adopted.
6.	Pre-submission interaction form should be possible before the LoI and Rapporteur appointment since some issues could be solved by the Product Lead, this will help Applicant to start preparing the dossier properly to meet the expected timeline.	MAA pre-submission interactions (PSIs) are aimed at providing applicants with information that will assist them in the finalisation of their upcoming marketing authorisation application, which is why PSIs are advised to be triggered around 6 months prior to intended submission date which should have been confirmed via the letter of intent. The EMA Product Lead is assigned when eligibility is confirmed, which generally is 18 months ahead of the intended MAA submission. Any questions can therefore be sent to the PL from that point onwards.

No.	Question proposed	Response
7.	Assignment of Rapporteurs earlier would help in dialogue and submission planning. SA is often unfeasible in this phase. Dialogue with FDA is easier to access leaving EU behind. What are your thoughts re this or intro of a pre-submission rapporteur role?	The comment is acknowledged and can be considered during the current revision of the pre-submission interactions with applicants.
8.	If we decide to apply for a clock stop extension and during the process the MAH anticipates the agreed submission deadline, how could we communicate this to Rapporteur?	It is important to communicate these changes as soon as possible and via the EMA procedure manager. Depending on how much notice is given, the Rapporteurs might not be able to accommodate, so the more notice the better.
9.	I was wondering- it was stated "no new data" during a submission / I would assume that means "no new data of a new trial" - however, new analysis of the prior submitted data would be acceptable - thx	Indeed, if the CHMP requests additional analysis to be performed, these are not considered to be new data.
10.	Will predictability improve for applicants with these new measures e.g. fewer delays with ARs, UARs etc? More engagement with clarification meetings.	That is indeed the expectation. With better submission predictability, the NCAs should be able to better resource and plan their work, leading to fewer delays in assessment reports and potentially greater availability for meetings.
11.	Which are the topics to be addressed to Rapporteur?	Applicants have the opportunity and are encouraged to meet with their appointed (Co)-Rapporteur and assessment teams at national level to present and discuss any scientific aspects of their upcoming MAA.
12	What is the best way to communicate delays for new indication submissions, via project manager /rapporteurs via mail?	Regarding extension of indication (type II variation), the PL serves as the main liaison between the EMA product team, the Rapporteurs and the MAH. A delayed of an expected EoI should be communicated to the PL as soon as possible.
13.	Mr. Alberto, fees for changes in intended submission date is it one time change in date, or will fees apply every time it is changed? And if yes, what will be the reference date for calculation of the second delay.	The reference date for all changes in the intended submission date is the date declared in the Letter of Intent. The fee applies to every change in due date where the intended date is beyond 60 days from the date declared in letter of intent.
14.	Product lead should be able to solve most of the issues for example the one related to validation issues, no need for Rapporteur, what do you think?	In terms of administrative validation issues, the Product Lead, in collaboration with the product team (other functions within the Agency) should be able to answer any questions. Applicants are encouraged to liaise with their appointed (Co)-Rapporteur and assessment teams at national level to present and discuss any scientific aspects of their upcoming MAA.

No.	Question proposed	Response
15.	Can you please explain if there were substantial gaps in the procedure of the application of Apellis for Pegcetacoplan that resulted in the negative CHMP Opinion?	We cannot comment on individual circumstances for individual procedures. Please refer to the EPAR available on the EMA webpage.
16.	One of the advantages of the European system is that it has been science driven. If there is ever increasing reduction in flexibility to allow for scientific uncertainty, this becomes a further barrier for EU competitiveness.	There is no problem whatsoever with scientific uncertainty. It is absolutely understood. However, it should not lead to procedural uncertainty.
17.	If I realise that I can anticipate the proposed submission date, is it possible? May I file the MAA before the proposal deadline? How many days before I have to communicate the change? Is there a procedure?	Any changes to the submission date indicated in the LoI must be communicated via an updated LoI. In view of an intended earlier submission Applicants are encouraged to notify the PL via e-mail as soon as possible. It is extremely important that any changes (delays or anticipations) are communicated as early as possible so that the NCAs can ensure that the resources will be available. If a submission is made earlier than intended and with no notice of change, we cannot guarantee that the Rapporteurs will be able to accommodate.
18.	Is the fee for changing submission date applicable to generics/ type II/ extensions/ hybrid applications as well?	The fee only applies for changes in submission date of initial MAAs.
19.	Would it be possible to have the possibility to pose question to EMA before the rapporteur appointment? Which nature?	The EMA PL is assigned once the eligibility to the centralised procedure is confirmed, which generally is 18 months ahead of the intended MAA submission. Any questions can therefore be sent to the PL from that point onwards.
20.	In terms of rationale for delay or cancellation, highlighting a failed bioequivalence study was cited as an example of poor communication presumably for a generic. What further details do you think should have been included?	More information about the reasons for delays will give the regulators a better understanding of the hurdles encountered during medicines development and hence the possibility to act upon it within their remit.
21.	Will the new fee regulation charge for submission delays still be charged if EMA/NCAs suggest delays at PSM?	The fee applies to all changes in due date. The new regulation does not establish any differentiation based on the justification or the reason for the date change.
22.	Could we make the eligibility definitive once it is granted?	Any application to the centralised procedure accepted under Article 3(2)b must be submitted within 18 months from the date of CHMP adoption, this is because the applicant needs to show that the medicinal product constitutes a significant therapeutic, scientific or technical innovation or that the granting of authorisation is in the interests of patients. Once this time has elapsed and no submission of the initial MAA has taken place, the applicant will be requested to

No.	Question proposed	Response
		submit a request to re-confirmation the justification and eligibility under Article 3(2)b. In exceptional cases, a maximum period of 3 years from the time of CHMP adoption might be accepted following appropriate justification from the applicant.
23.	In case of DCPs, we have been seeing delays in procedure restart due to workload at the RMS. Therefore, it is becoming difficult to predict approval timelines. Any advice for the applicants? Thank you!	The Swedish MPA normally checks the draft responses and plan for restart within the stipulated six weeks. However, we often find that the draft response is not complete, which will lead to delays in procedure restart. Also, given the unpredictable inflow of submissions, we may occasionally need to delay the restart due to the difficulty to plan resources.
24.	How is this discussion being linked to the oncology pathfinder? There are specific challenges in oncology. Consider event-based studies and inherent uncertainty around timing. Are the nuances of TA considered?	With the Oncology Pathfinder, we hope to be able to try out some novel approaches. The intent is that any changes to process that have been pioneer with Pathfinder will become the norm for all products going forward.
25.	How were the delay fees calculated? Are the fees for delays proportional to what might be saved/gained from submitting an immature application and then delaying it?	The new fee regulation was based on a cost analysis exercise. The fee will cover any administrative actions at EMA and NCA level derived from the change in due date.
26.	What about using work sharing with other international agencies and reliance?	EMA is exploring a number of different opportunities for collaboration with third country agencies. We are promoting the use of OPEN, using the EU-M4All procedure and we are also observers in Project Orbis.
27.	Is the meeting with the rapporteurs really encouraged? The guideline currently states it is possible only in cases where it is not possible to solve in writing through the pre-submission form.	Currently companies are encouraged to meet with the Rapporteurs ahead of filing. There is also an opportunity for a pre-submission meeting with EMA, however for straightforward applications, exchange in writing is preferred. The Focus group on revamping the pre-submission interactions will look into possible improvements that could be made.
28.	What percentage of CP MAAs received on time would EMA like to see? 100% predictability is not achievable to due to risks inherent to every development. What would you like to target?	Currently the percentage of products that are submitted on the date indicated on the Letter of Intent is between 30 and 40%. If we could revert this and make it so that 60-70% are received on that date, while 30-40% are delayed, that would be a great improvement.
29.	Could that barrier towards continuity of expertise be solved with legislation? Bring in the expertise earlier as is done as a best practice in other regions. Is this something raised by EMA/HMA in legislation discussions?	The new legislative text put forward by the Commission does put a lot more emphasis on pre-submission interactions. This is something that EMA is looking into alongside all other aspects of the new legislation.

No.	Question proposed	Response
30.	Could you comment on whether you can attest to a correlation between the extent of the observed bad practices and the size or maturity of the enterprise applying for the authorisation?	We could not identify a correlation with the size of the enterprise.
31.	Will same rapporteur be named for one Company, or will there always be other rapporteurs named?	Upon a change in a due date, the maintenance for the same Rapporteur cannot always be guaranteed.
32.	Hi everyone, will you put in place a special regulation and submission process (with rolling reviews) related to medical counter measures development as the Covid-19 model (applied to the future outbreaks, for example: Mpox).	In the new proposed legislation, there is a provision for a "phased review", which, like the rolling review, would allow companies to submit the dossier in different parts, thereby allowing the assessment to begin before the package is complete. This would not apply to all procedures but, as currently described in the proposed text "For medicinal products that are likely to offer an exceptional therapeutic advancement in the diagnosis, prevention or treatment of a life-threatening, seriously debilitating or serious and chronic condition."
33.	Do you recommend having pre-submission meetings also for type II variations to extend the therapeutic indication, especially if the submission is planned with interim data.	Pre-submission meetings are indeed possible for extension of indication submissions. And indeed, for situations where the planned submission is based on interim data, it may be prudent to discuss with the Rapporteurs. It will of course depend on the timing of such a meeting request (the more notice the better) and the availability of the Rapporteurs.
34.	Where can we find guidance regarding assignment of CHMP rapporteurs vs previous scientific advice rapporteurs?	This aspect is not currently covered in EMA external guidance. The aspect is considered to be reflected in the next revision of the Procedural Advice on CHMP/CAT/PRAC Rapporteur/Co-Rapporteur appointment principles, objective criteria and methodology in accordance with Article 62 (1) of Regulation (EC) No 726/2004
35.	I am here in the EU. I found a lack of any timeliness or consistency in my POC for my product description according to instructions. It costs. Is there an alternative? I had the opposite from the FDA which proceeded w a positive experience	Apologies, it is not entirely clear what you are referring to. If you are referring to an experience of interaction with EMA, we are sorry that it was not a positive experience. Depending on what the particular situation was, we would welcome feedback via the appropriate channel for that particular interaction.
36.	Can you please provide your views on delays (beyond the procedure timetable timelines) in the assignment of (co-) Rapporteurs and the impact it could have on submission predictability?	Upon a change in a due date, the maintenance of the same Rapporteur and Assessment team cannot always be guaranteed. The maintenance or total/partial replacement of the assessment teams will be linked to the availability of expertise for the new intended date. We expect that the reappointment of assessment teams that normally takes one month at least, does not impact the

No.	Question proposed	Response
		new proposed submission timelines and the predictability.
37.	Can you please comment regarding accelerated evaluations - with respect to clock stops - submission of additional information etc as you have already done for standard review timelines	If a product is being evaluated under accelerated assessment, the timelines for clock-stops are shorter than for standard evaluations. For example, for the first round of questions (at D90) the clock stop is 1 month only. Should the company require more time, the timetable is then likely to shift to a standard one, to allow the Rapporteurs sufficient time to complete the assessment of the presumably lengthy or data heavy responses. On the other hand, should the applicant plan to submit responses in a shorter timeframe than the guidance allows, this should be discussed with the Rapporteurs' as early as possible, even at the time of pre-submission meeting, if applicable.
38.	It was stated "no new data". What if new data become available while the assessment is ongoing, and they can be useful to properly answer to ema question at day 120?	The submission of any substantial amount of data in the responses to the D120 list of questions is discouraged, unless of course expressly requested by the CHMP. This is because the Rapporteurs have limited time, after the receipt of responses, to complete their assessment. Companies should not plan a priory to submit an MAA with interim or incomplete data and expect to be able to complement with the D120 responses. Any such discussions should also take place, prior to submission, with the Rapporteurs and EMA.
39.	On practical point, EMA already request pipeline forecast in Jan and June. now in addition we have NCAs. can EMA establish an efficient system of planning? that maybe can be updated along the way? Maybe using EMA Iris Portal or else?	Yes, there is such plan. In future it will be possible to use IRIS portal for planning purposes.
40.	I always found that the pre-submission meeting and rapporteur meeting good interactions to help confirming the submission date. But those meeting are scheduled to close to the submission date. Could we move that opportunity earlier?	Even with the appointment of Rapporteurs 6 months ahead of submission, it is sometimes challenging to schedule a pre-submission meeting in good time. This is one of the aspects that the Focus group on revamping the pre-submission interactions will look into.
41.	In relation to the twice-yearly requests for feedback on all planned submissions, it would be very helpful if these requests included a template from EMA.	This feedback has been received and the new notification, which will be sent on 1st November, will include a template table.
42.	Re fees: Is the fee still charged even if we have a very good justification for delay? We are missing details here on applicability. Also, if we send a	The date declared in the first Letter of intent determines the date of submission for fee calculation purposes. Submission of a revised letter of intent with a new due date is equivalent to a request of change in submission date.

No.	Question proposed	Response
	revision to LoI the new date is the reference?	
43.	In oncology where OS is expected to be the endpoint to assess the B/R, the submission date will be driven based on the number of events which may be a challenge to predict and lead to changes. What is the view of Rapporteurs?	We understand the difficulty to plan for these submissions, however the planning often seems to be built on overly optimistic predictions. Any assumptions/predictions regarding submissions dates should be realistic and not only best-case-scenarios and should also consider the time needed to finalize all necessary documents/reports to be included in the dossier once the study results are available. Best practice should be to inform EMA/Rapporteurs as soon as possible on any anticipated changes of submission date.
44.	If the application submitted earlier than the intended date (perhaps more than 60 days earlier than the intended date), does the applicant also need to pay the intended date change fee?	This situation is rather infrequent. The legislation refers to the changes in due date, both earlier and later submissions.
45.	If the Letter of Intent is submitted in 2024 but there is then a delay to 2025, will the new delay fee apply?	The fee covering pre-submission activities becomes due at the time of receipt of the Letter of intent. The fee for changes in submission date becomes due at the time of receipt of the request for a change in submission date. Both fees will enter into force from 1.1.2025. A letter of intent received in 2024 for product A will not trigger any fee for pre-submission activities. However, any change in submission date requested for product A submitted in 2025 or later date will trigger the fee for change in due date (provided that the new submission date is more than 60 days from the date declared in the letter of intent).
46.	Especially for SMEs, the administrative aspects of an MAA are very burdensome and put strain on limited resources. Is there any attempt to streamline this or provide more flexibility for SMEs?	The requirements for submissions are the same for all applicants. It is understood that some aspects are more challenging for smaller companies, but we do not intend on creating a two-tear system. We have dedicated functions that offer support to SMEs.
47.	If I submit a pre-submission request in 2024 and then I changed it in 2025, is the new fees regulation applicable? In other words, it is applicable to the pre-submission request just starting in 2025?	The fee covering pre-submission activities becomes due at the time of receipt of the Letter of intent. The fee for changes in submission date becomes due at the time of receipt of the request for a change in submission date. Both fees will enter into force from 1.1.2025. A letter of intent received in 2024 for product A will not trigger any fee for pre-submission activities. However, any change in submission date requested for product A submitted in 2025 or later date will trigger the fee for change in due date (provided that the new submission date is more than 60 days from the date declared in the letter of intent).
48.	This is still unclear why additional fees will apply if there is a very good	The fee applies to all changes in due date. The new regulation does not establish any

No.	Question proposed	Response
	justification for delay. Can we get more details please	differentiation based on the justification or the reason for the date change.
49.	Is there any example of joint pre-submission interactions between EMA and FDA having an impact on submission predictability (i.e. causing postponement of initially agreed submission date to EMA)?	We do not currently hold join pre-submission interactions with FDA. We are aware of some cases in which either due to a request from FDA or from the EMA Rapporteurs, applicants have chosen to postpone their submission. This is not a problem, provide this change is communicated as soon as possible to us.
50.	Comment: As a regulatory professional thank you for helping me appreciate the regulators perspective which will help with promoting visibility with regards to submission timings and workload management for HAs.	We are delighted you found the workshop beneficial and will help promote the importance of reliable submission dates.
51.	How does EMA ensure alignment and consistency across various Member State' requirements to avoid unexpected delays or deviations during the review process?	The requirement for the centralised procedure is the same, regardless of who the Rapporteurs are. In addition, the fact that all products are ultimately discussed in CHMP, ensures that there is consistency in the review process.
52.	Again, efficient system/tool shared between EMA, NCA and industry would be welcomed. there are probably thousands of emails going around, so information can also be missed easily from all sides.	In the next year or so, all the processes related to the centralised procedure will move to IRIS. Indeed, the IRIS platform will allow for faster and more direct exchanges of documents and will replace the current use of Eudralink.
53.	Fee requirements will negatively impact more the small medium Industries than the big pharma	The comment is acknowledged. The current fee regulation does not foresee any incentives for SMEs applicable to the fee on change in date of submission.
54.	Is that penalty calculated on the first letter of intent?	Ye, the fee is triggered from any changes in submission date beyond 60 days from the first LoI.
55.	If I can wrap up all presentations, the best procedure is to submit the LoI 3 months before the submission.... not 7 months. In the first scenario, the odds of a delay are low	We do not encourage this at all. In fact, submitting the Letter of Intent closer than 6 months to the submission date, puts the system under more pressure. Rapporteurs are not assigned until the Letter of Intent is received and with such a late submission the risk of not having Rapporteurs ready is high. In addition, assuming the applicant would like to engage with the Rapporteurs and EMA ahead of the submission, there would be no time to do so.
56.	Please could you comment on how SMEs who don't have the same resource available are supported through this process?	The comment is acknowledged. The current fee regulation does not foresee any incentives for SMEs applicable to the fee on change in date of submission.

No.	Question proposed	Response
57.	Is the fee only applicable for the delayed submission? What if the applicant submits earlier than the intended date? Because I believe earlier submission by the applicant also impacts the assessment teams schedules.	The legislation refers to the changes in due date, both earlier and later submissions.
58.	Do you have experience that one authority is asking for the questions already raised from another authority, where approval already happened? Or do they directly contact each other after approval?	Unless we are actively participating or observing in a process such as OPEN or Orbis, we do not share assessment reports with other third country agencies, nor are we aware of the questions that they might have raised in the context of a product assessment.
59.	What about type II variations and line extensions which are now facing delays from EMA due to "resource constraints." (Several examples available). How is EMA also implementing best practices to keep submission predictability at their end?	Delays in post-marketing procedures are in essence a result of poor predictability of submissions in general. We are trying to promote good adherence to letter of intent dates, and we are now proactively collecting post-marketing submission plans for MAHs. The intent is that these activities will holistically help the network to be able to cope with the volume of incoming work.
60.	In an environment where industry is striving to reduce the time from data to submission, which leads to pre-submission interactions prior of knowing the results, what is EMA view on this? And what are your suggestions for efficient pre-submission interactions?	Pre-submission interactions with EMA can be triggered before the results are known to assist in the finalisation of the upcoming marketing authorisation application. In relation to content/scientific data, it is indeed challenging to have meaningful interactions where no data are available. It can be helpful, if time allows, to have the pre-submission meeting once at least as top-line data become available. Alternatively, the company can consider the option to schedule a placeholder meeting, taking into account when the results are anticipated. It should also be noted that the rapporteurs and their assessment teams need time to look into the pre-submission meeting background documents to proceed with a productive meeting. The Focus group on revamping the pre-submission interactions will look into possible improvements that could be made.
61.	Another solution could be a mandatory pre-submission meeting to discuss the dossier completeness and after that agree with the rapporteur and EMA the submission date	This would indeed be a possible way forward. Hopefully, it will be discussed in more detail when the formal focus group on revamping the pre-submissions is launched in 2025.
62.	Industry would prefer 7 months for all the reasons stated but there would be a higher likelihood of a fee delay charge, so what is the industry incentive to file earlier?	The LoI filing at 7 months prior to the intended submission date is organised in that way in order to allow Rapporteur appointment around 6 months prior to submission to allow for useful interactions between applicants and EMA/Rapporteur ahead of submission. Filing the LoI later runs the risk of Rapporteurs not being appointed in time and would also not give enough time for pre-submission interactions which are

No.	Question proposed	Response
		beneficial to all parties. The Focus group on revamping the pre-submission interactions that will kick-off in 2025 will explore possible alternatives to the current way of working.
63.	Considering the complexity of innovative medicines, how could reliance procedures between the EMA and other regulatory agencies be structured to effectively reduce the workload on health authorities?	EMA is exploring a number of different opportunities for collaboration with third country agencies. We are promoting the use of OPEN, using the EU-M4All procedure and we are also observers in Project Orbis.
64.	Can the LoI be submitted earlier to have rapporteur appointed earlier than foreseen by the guideline?	Currently, the process is that Rapporteurs are appointed 6 months prior to the intended submission date. Therefore, sending an LoI early would not change the timing. Together with the Focus group on submission predictability, and in 2025 with the Focus group on revamping the pre-submission interactions, we will explore potential changes to these processes that would ensure an overall better predictability of submissions.
65.	Agree that key message is that early planning and iterative dialogue is important. Pushing communication to later will not help. Continuity of dialogue through development and into decision making will optimize efficiency for everyone.	Agreed.

6. Glossary

AR	Assessment Report
CP	Centralised procedure
CHMP	Committee for Medicinal Products for Human Use
CTD	Common Technical Document
DCP	Decentralised procedure
EMA	European Medicines Agency
EU	European Union
EoI	Extension of Indication
HMA	Heads of Medicines Agency
GCP	Good Clinical Practices
GMP	Good Manufacturing Practices
LoI	Letter of Intent
LoQ	List of Questions
LoOI	List of Outstanding Issues
MAA	Marketing Authorisation Application
MAH	Marketing Authorisation Holder
MNAT	Multinational Assessment Team
MRP	Mutual recognition Procedure
MS	Member States
NCA	National Competent Authority
NDA	New Drug Application
Q&A	Questions and answers
PL	Product Lead
PAR	Preliminary Assessment Report
PSIs	Pre-submission interactions
PSM	Pre-submission meetings
SA	Scientific Advice
SAT	Single arm trial
SME's	Small and medium-size enterprises
UAR	Updated Assessment Report
US	United States

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