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FGSP final report 16-Apr-24

ANALYSIS AND RECOMMENDATIONS FOR IMPROVEMENT

Final report

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1. Introduction

Unreliable long-term planning for initial marketing authorization 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 by the COVID-19 pandemic. The results of an internal investigation were presented at the *7th Meeting of the industry stakeholder platform on the operation of the centralised procedure for human medicines* in December 2021 ([link](#)). During the follow-up discussion at the *8th Meeting of the industry stakeholder platform on the operation of the centralised procedure for human medicines* in June 2022 ([link](#)) 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 representatives¹, started its work in November 2022.

2. The work of the focus group

To confirm the preliminary analysis on historical data it was decided to proactively monitor the 2023 MAAs pipeline. To this end all applicants that have indicated an MAA submission date in 2023 were contacted in December 2022 to make them aware of both this proactive monitoring and to request the confirmation of their planning on a 2023 submission. Monthly submissions received in 2023 were compared with the projections provided at the end of the previous year. The focus group met regularly throughout the year to analyse the results of this monitoring.

2.1. The monitoring

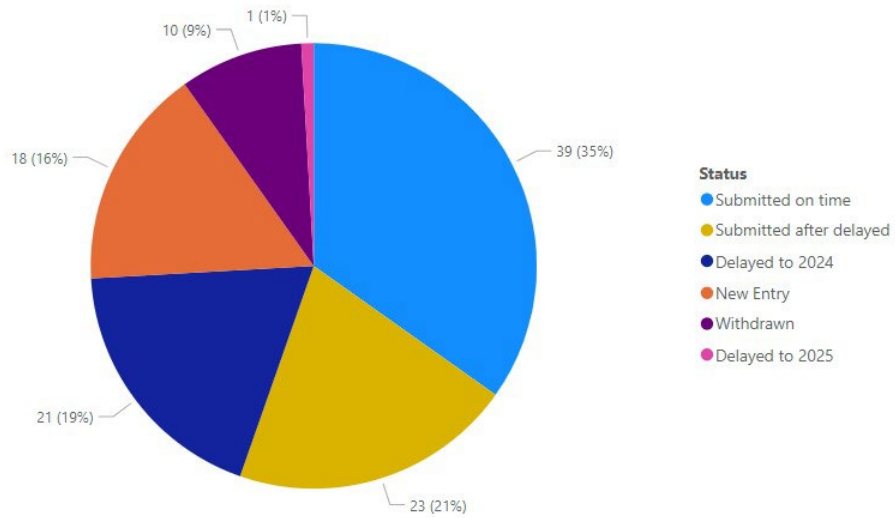
The focus of our analyses were the projections of MAAs with a letter of intent (LoI) as this is the latest document required before submission and triggers the rapporteurs' appointment.

The outcome of the monitoring is summarised below.

¹ The focus group is formed by representatives of EMA, CMDh, CHMP, PRAC, CAT, EFPIA, EUCOPE, EuropaBio, Europharm, Vaccines Europe, and Medicines for Europe

Fig. 1 2023 MAAs submission trend compared with the forecast issued in December 2022.

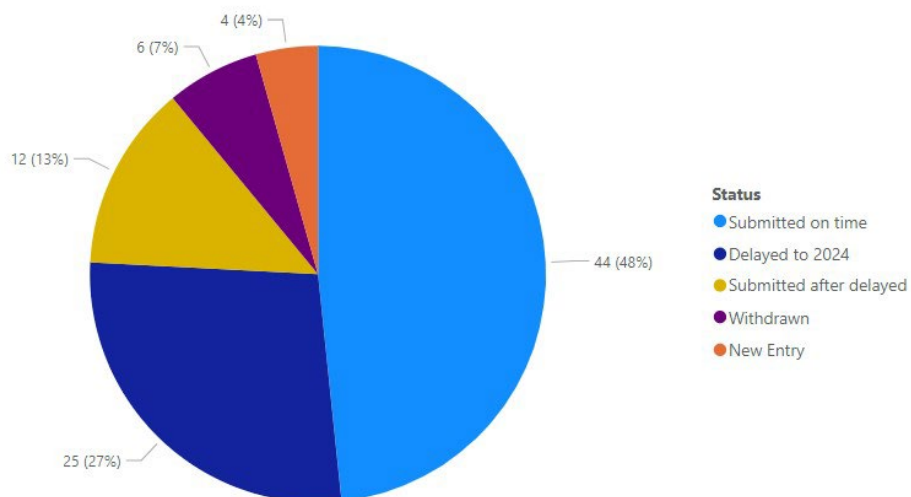
2023 MAAs pipeline with Lol (n = 112)



The percentage of MAAs submitted within the year is 56% but only 35% of the applications are submitted on time, the remaining 21% is submitted with a delay. Another 30% of the pipeline is either withdrawn or postponed to the following year. The new entry category represents the MAAs not included in the forecast but nonetheless submitted, and it comprises mainly generics applications. The data concern only MAAs with a LoI when the forecast was issued.

Fig. 2 MAAs submission trend in the second part of 2023 compared with the forecast issued in June of the same year.

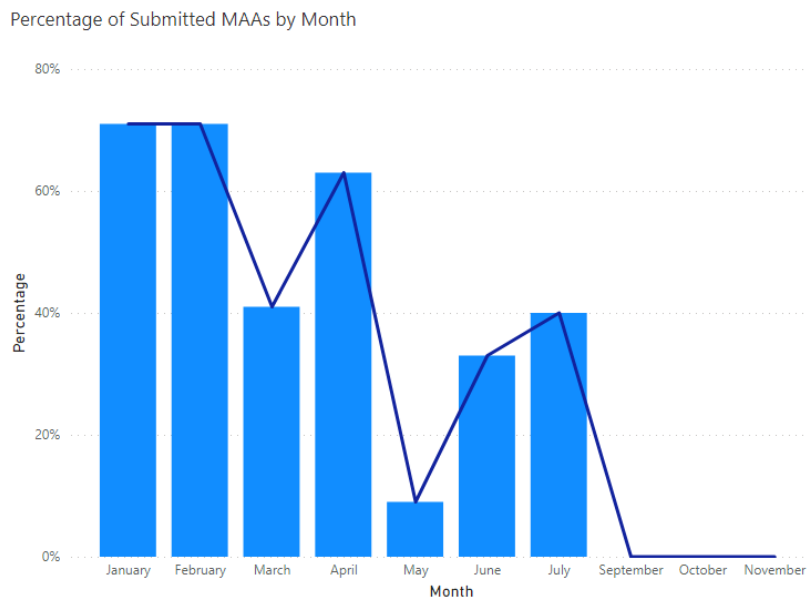
H2-2023 MAAs pipeline with Lol (n = 91)



To assess the precision of the forecast issued closer to the planned submissions we have compared the submission received in the second half of the year with the projections available at the mid-year timepoint. If the precision of the forecast improved, with 48% of the MAAs submitted on time, we still

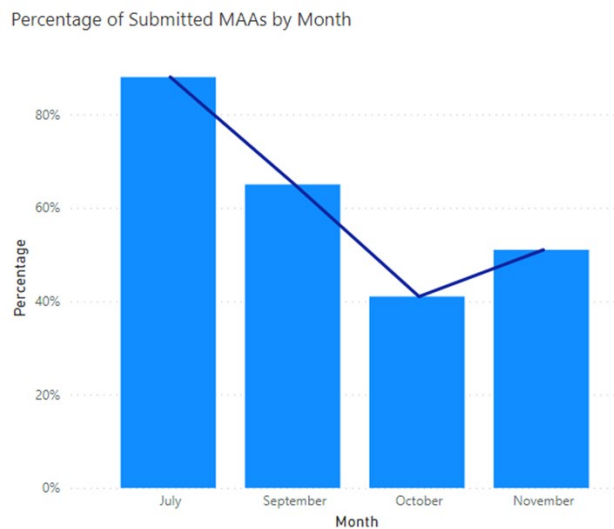
observe some delays before submission (13%) and a considerable number of applications postponed to the following year. All MAAs had a LoI when the forecast was issued.

Fig. 3 Monthly monitoring of the MAAs received in 2023 (baselined to December 2022).



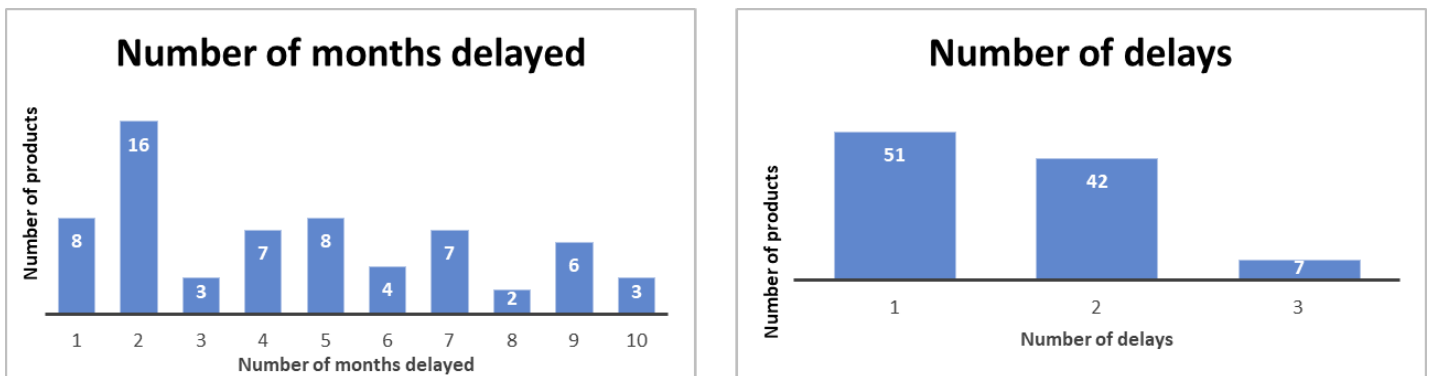
MAAs are submitted following predefined timetables. We have monitored these monthly submissions. The graph above shows the trend in the monthly submissions compared to the projections available in December 2022 for MAAs with a LoI. It is evident how the precision is drastically decreasing the further we are from the forecast time point.

Fig. 4 Monthly monitoring of the MAAs received in the second half of 2023 (baselined to June 2023).



To assess the behaviour of the monthly MAAs submissions in the short-term we have compared the applications received in the second half of the year with a new baseline available in June 2023. All MAAs had a LoI when the forecast was issued. Despite the shorter time point from the forecast the submissions' precision still present similar trend observed in the yearly assessment.

Fig. 5 The extent of the delays observed within the year at the Q3-23 timepoint revision.



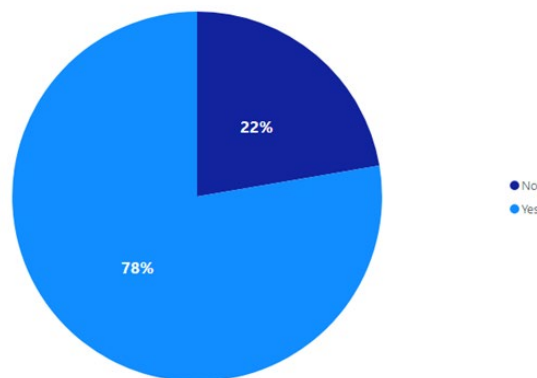
To measure the extent of the delays and hence the workplan disruption of the regulatory network, we have captured the number of months of delays together with the number of delays within the year affecting the MAAs pipeline.

Figure 5 quantifies the delays observed within the MAAs pipeline during the analysis performed at the Q3-23 timepoint with December 2022 as baseline. The panel on the left depicts the number of months of delays while the panel on the right maps the number of times a MAAs was delayed within the year. It is evident how the pipeline is disrupted both by the length and frequency of the delays.

MAAs may be delayed by several months and often more than once.

Fig. 6 Percentage of responders to the EMA request for submission date confirmation.

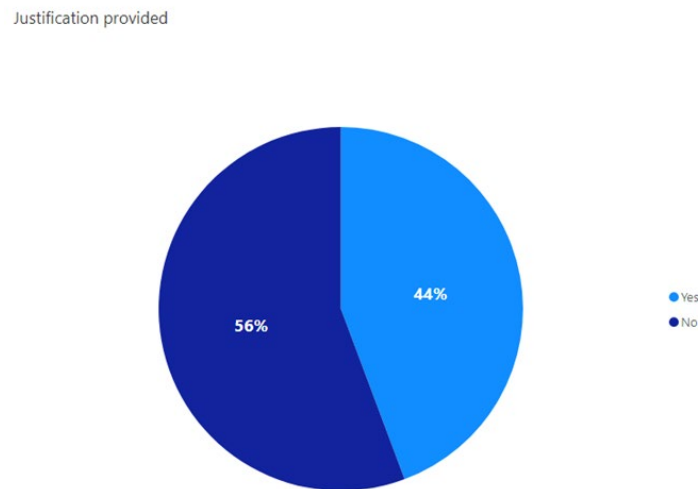
Industry replied before submission



One of the measures in place to plan the workload of the regulatory network is an automatic email to the prospective applicants sent three months prior to the planned submission date to request confirmation of the plan.

The pie chart in Figure 6 highlights how most of the applicants do respond to the request but the percentage of non-responders is still high.

Fig. 7 Percentage of responders to the EMA request for justification of the change in submission plan.



Together with the request to confirm the planned submission, in the automatic reminders sent out to the applicants the Agency is asking also for the justification in case of change in the submission plan. Receiving this information is important to understand what measures could be put in place to modify the poor predictability trend observed so far.

As depicted above in this instance the percentage of responders is much lower, slightly more than 40%.

Moreover, the few justifications received are not informative on the real reasons for the change in plan so give no input to find possible solutions to rectify the submissions' trend.

2.2. Proposed recommendations

Based on the data collected throughout the year, the focus group drafted a few possible solutions to improve the MAAs submission precision and the regulatory network preparedness:

To improve preparedness:

- Use pre-submission interactions to discuss submission plans and the maturity of the dossier.
- EMA to contact the applicant to request plan for major post-authorization submissions linked to the MAA (e.g. Extension of Indications & Line extensions).
- Implement annex to the revised LoI with requested information relevant to ascertain certainty and potential evaluation challenges (e.g., plan to request accelerated assessment, novel clinical trial, new methodology, date of clinical database lock, scientific advice, etc.).

To improve submission predictability:

- Modify the text in the current LoI to make clear to the applicant that resources are booked according to the data provided in the document (ring-fencing resources).
- Appoint Rapporteurs 3 months before planned submission, instead of the current 6 months - to be paused for the time being, to be implemented if other measures prove inefficacious.

To improve workload management:

- Remove rapporteurs if no reply to EMA's automatic reminders and consequent removal of the product from the pipeline – currently under discussion at EMA, to be implemented if other measures prove inefficacious.
- Reconfirmation of rapporteur appointment if delay is more than three months.

To improve communication:

- Training on the significance of the revised LoI and consequences for tying up network resources.
- Stress the importance to promptly reply to EMA requests for submission confirmation and to have a reliable contact point for the applicant.
- Importance to communicate planned post-authorization submissions (e.g., EoIs & LEs²)

Best practice:

- Update pre-submission Q&A to highlight need for open communication.
- Organize workshop to applicants on best practice for pre-submission of MAA.

2.3. Conclusions and next steps

Despite the active communication with applicants and the close monitoring exercised during 2023, the trend in the submission predictability did not deviate significantly from what observed in previous years ([link](#)).

The observation prompted the focus group to devise more active measures to improve the submission predictability.

There was consensus within the focus group on the choice of measures to be adopted as first option already in 2024 and on those to be temporarily paused.

As the current pharmaceutical legislation limits the enforcement of stricter measures, emphasis was given to the preparedness of the network and the communication activities therefore it was agreed to implement immediately the following measures:

- Pre-submission interactions should be strengthened to discuss submission plans and the maturity of the dossier. EMA has established a dedicated project; industry will be asked to nominate representatives.
- Applicants will be systematically contacted to request plans for major post-authorization submissions linked to their MAs. Automated emails will be sent from June 2024.
- The revised LoI has been enriched with new annex containing information relevant to ascertain certainty and potential evaluation challenges.
- Training will be reinforced to raise awareness on the importance to promptly and transparently communicate any changes from the submission plan should be justified; this may include dedicated webinar and amendments of the pre-submission guidelines.

It was deemed as well important to keep the monitoring of the MAAs pipeline ongoing and to be vigilant to the effectiveness of the measures implemented during 2024 so to escalate the network response if current poor submission predictability persists.

² EoIs = Extension of Indications; LEs = Line extensions

The focus group will therefore continue its monitoring activity and predictability assessment, with the plan to meet regularly to discuss the progress of the MAAs submitted during the current year. A more systematic monitoring, such as the one carried out in 2023, might be repeated in 2025 to determine with more granularity the effectiveness of the measures implemented.