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EUROPEAN MEDICINES AGENCY

Joint HMA/EMA multi-stakeholder workshop on submission predictability

25 September 2024 09:00-13:30 (CET)

Welcome by the Chairs

Fran Day and Aimad Torqui

Housekeeping

To avoid background noise, your **microphones will be muted** automatically upon entry into the virtual meeting room

If you would like to speak, please **raise your hand** and wait for the Chair to give you the floor. When given the floor, please state your name and affiliation.

Please be aware that the **chat function** is not available for this meeting.

Participants may be able to ask **questions or share feedback via Slido**, with the option of remaining anonymous*.

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Agenda outline

- Welcome and opening speeches – *E. Cooke, K. Broich*
- EMA Statistics on Submission Predictability and problem statement – *E. Tognana*
- Best Practice approach using current guidance – *J. Oliva*
- Views & concerns from Member States on Submission Predictability – *I. Landberg, G. Waxenecker*
- Update on Rapporteur appointments – *A. Ganan Jimenez*
- Q&A session - *All*
- Industry representatives' viewpoints on submission predictability – *P. Franco*
- Case studies: Innovators, Generics and Biosimilars – *Industry representatives*
- Panel Discussion: Q&A Exchange of Ideas - how can we improve submission predictability? - *All*
- Closing remarks – *F. Day, A. Torqui*

Opening remarks

Emer Cooke - EMA Executive Director

Karl Broich – President of BfArM

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EMA statistics on submission predictability and problem statement

Data and trends for submission predictability

Enrico Tognana
Senior Business Intelligence Specialist

Outline of topics

1. Data and trends for submission predictability
2. 2023 close monitoring exercise and results
3. Case studies – examples of good & poor submission planning

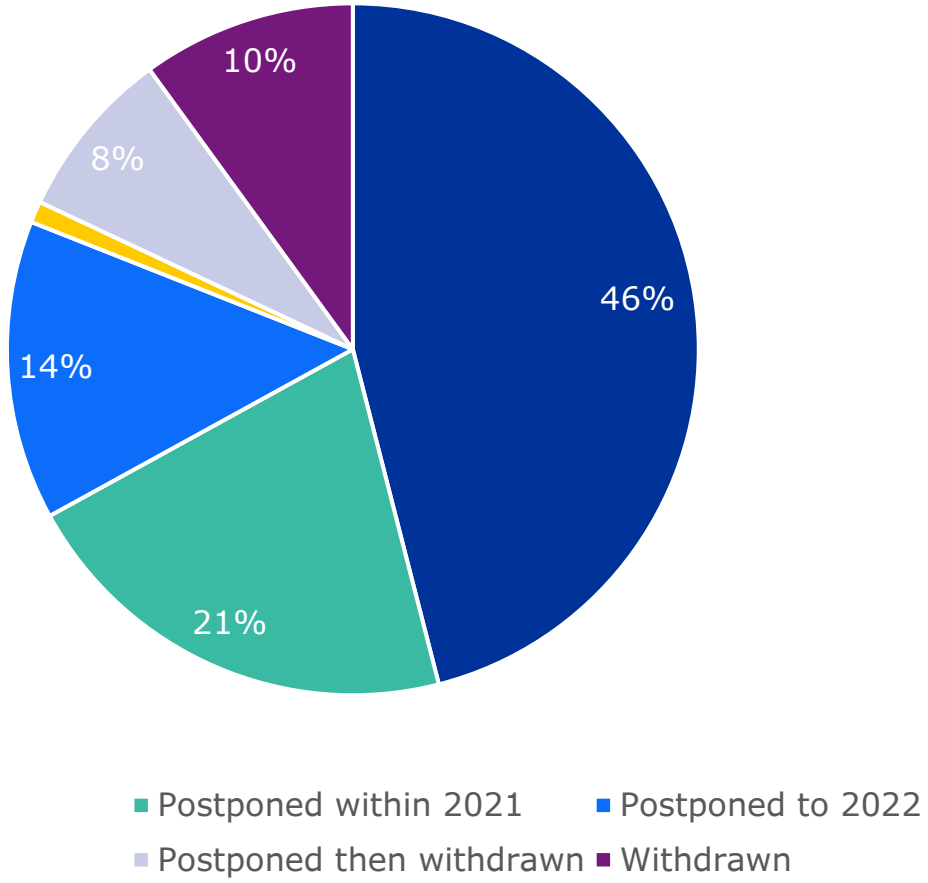
1

Data and trends for submission predictability

THE PROBLEM

Unreliable long-term planning for initial marketing authorization applications (MAAs) for centralized 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 departure of the UK from the system and the loss of staff due to burn-out during the COVID pandemic

Submission timeline for MAAs with LoI

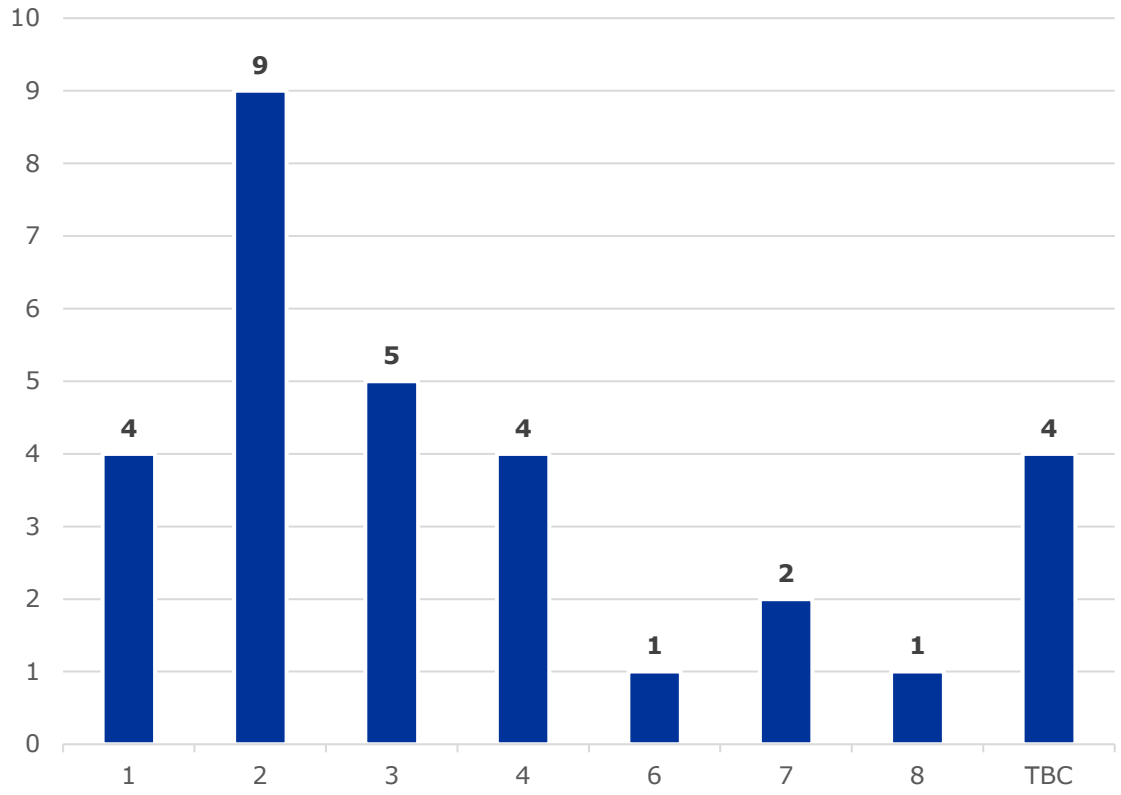


The problem - 2021 as an indicative example

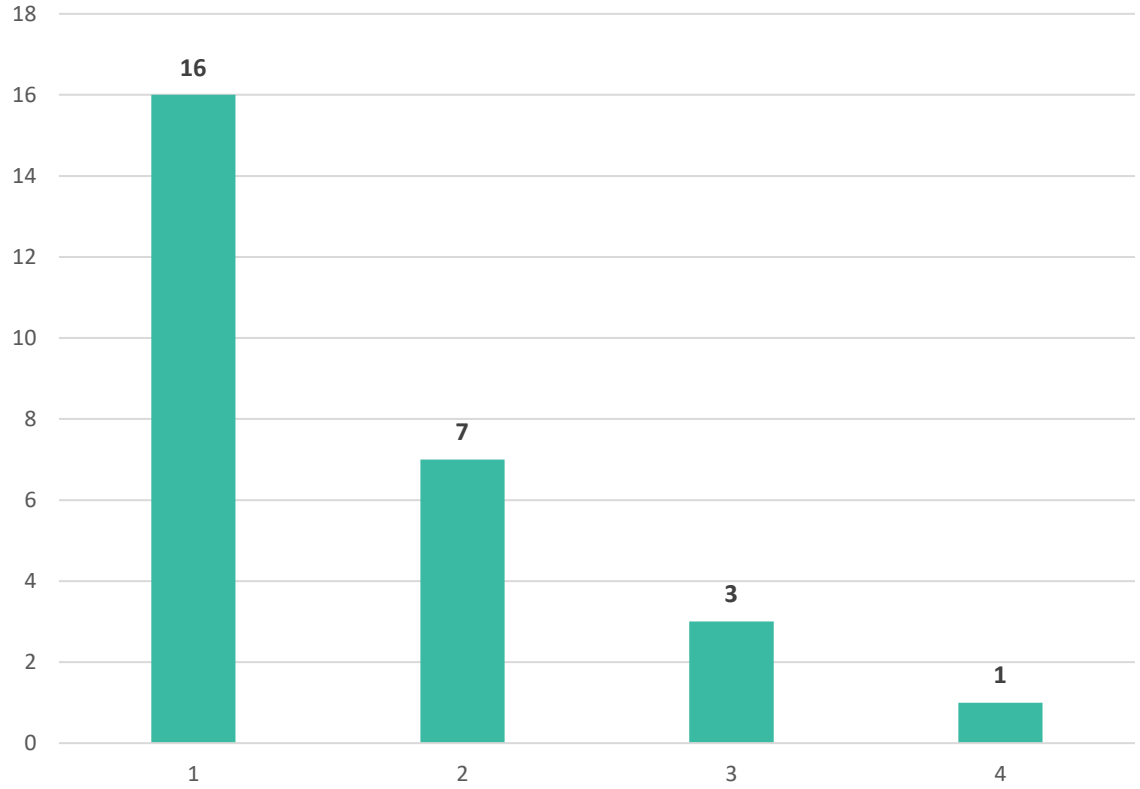
- These data show the actual submissions of initial MAAs in 2021 versus what was projected in Dec 2020
- All the submissions had a Letter of Intent (LoI)

The extent - delays within 2021

Months of delay accumulated by MAAs within the year



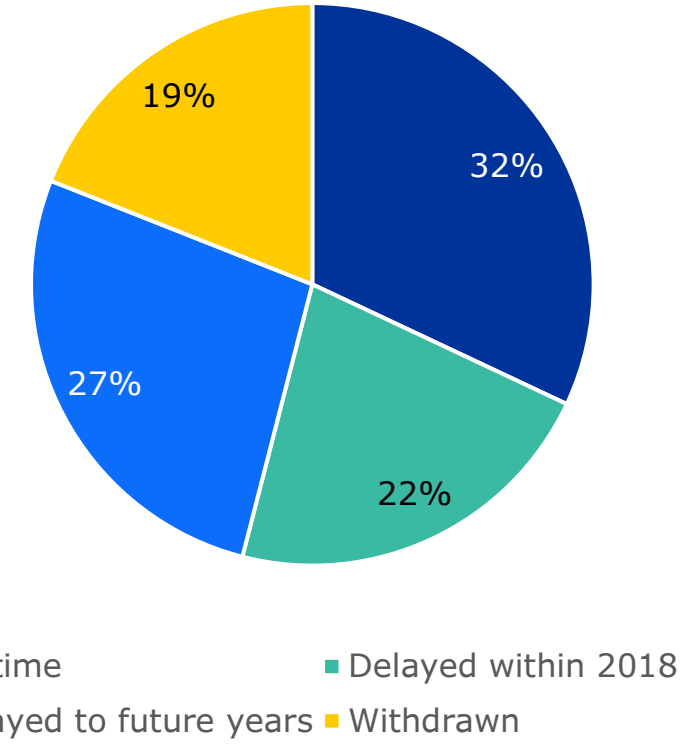
Number of delays accumulated by MAAs within the year



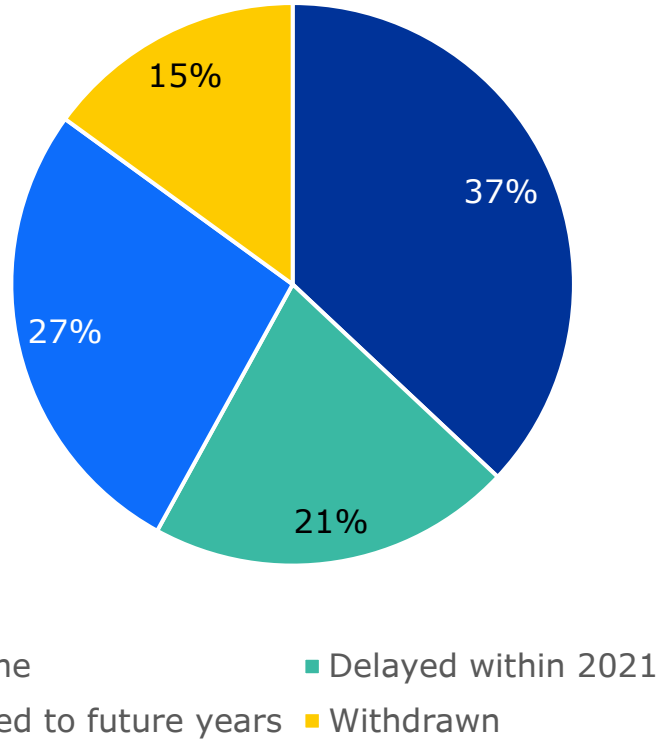
Was COVID-19 to blame?

COMPARISON OF PIPELINE BEHAVIOUR

2018 before coronavirus pandemic



2021 during coronavirus pandemic



2

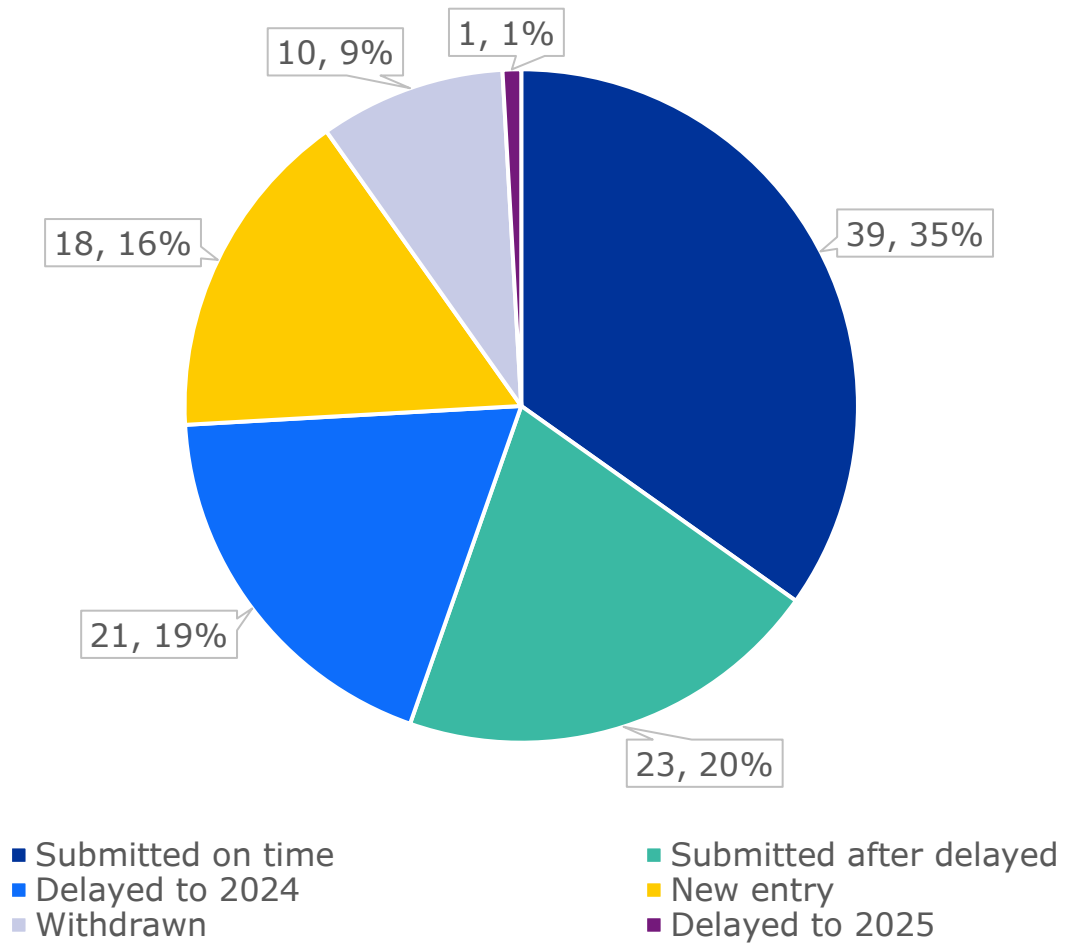
2023 close monitoring exercise and results

2023 MAAs pipeline - Planned & ad hoc monitoring

All Applicants that have indicated an MAA submission date in 2023 were contacted in **December 2022** to:

- Confirm that they are still planning on a 2023 submission (with exact date)
- Inform applicants that their planned submission would be tracked
- Automatic reminder **three month before planned submission**
- **Every quarter** the planned submissions were checked against the received submissions
- Applicants who failed to submit or change their submission date were asked to give a rationale
- In March **ad-hoc follow-up** for Applicants who did not provide justification
- In May **ad-hoc reminder** to Applicants still planning to submit MAAs in 2023 but still with no LoI
- The hope was that the active monitoring will in itself deter multiple changes

2023 pipeline monitoring

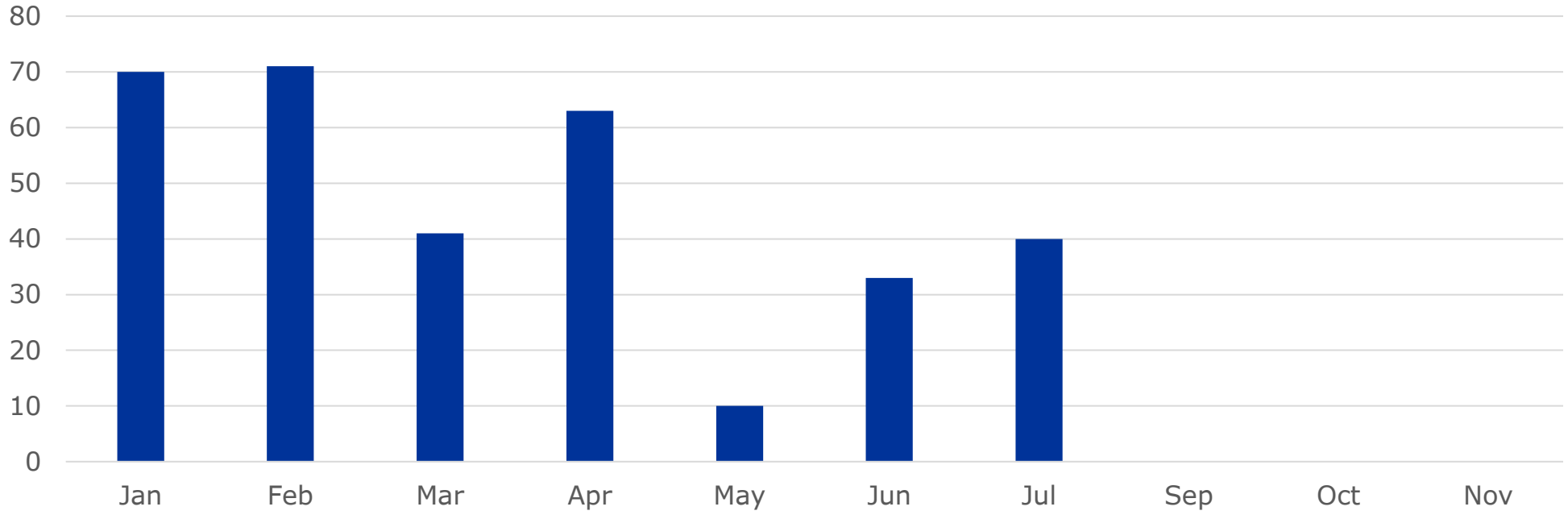


Forecast vs. actual

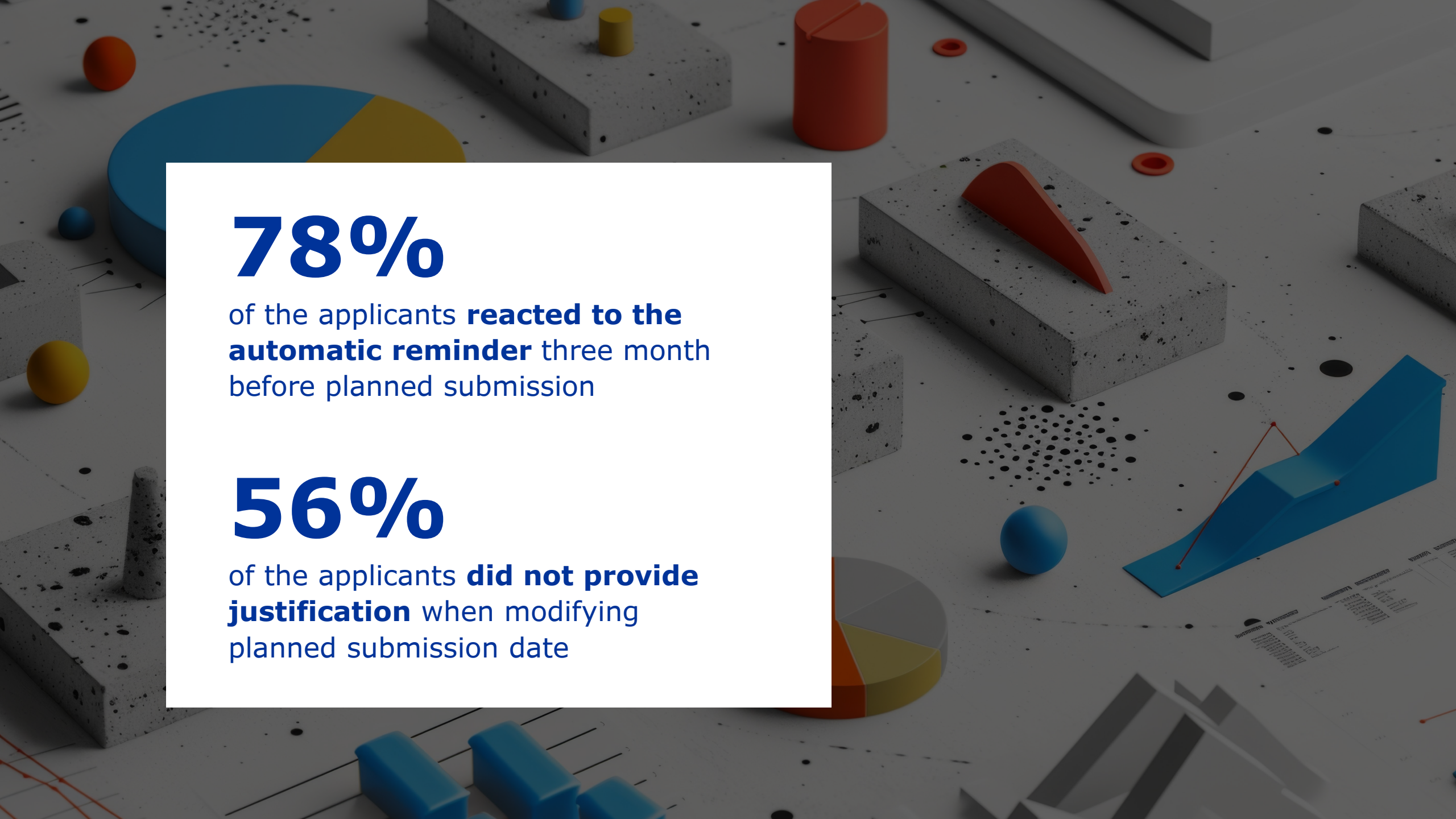
Actual submission of initial MAAs in 2023 versus what was projected in December 2022 with a Letter of Intent

The monitoring of planned submission during 2023

Percentage of submitted MAAs by month



The monitoring using June as cut-off showed similar trend. The details of the analyses are available in the final report of the *Focus group on submission predictability*.



78%

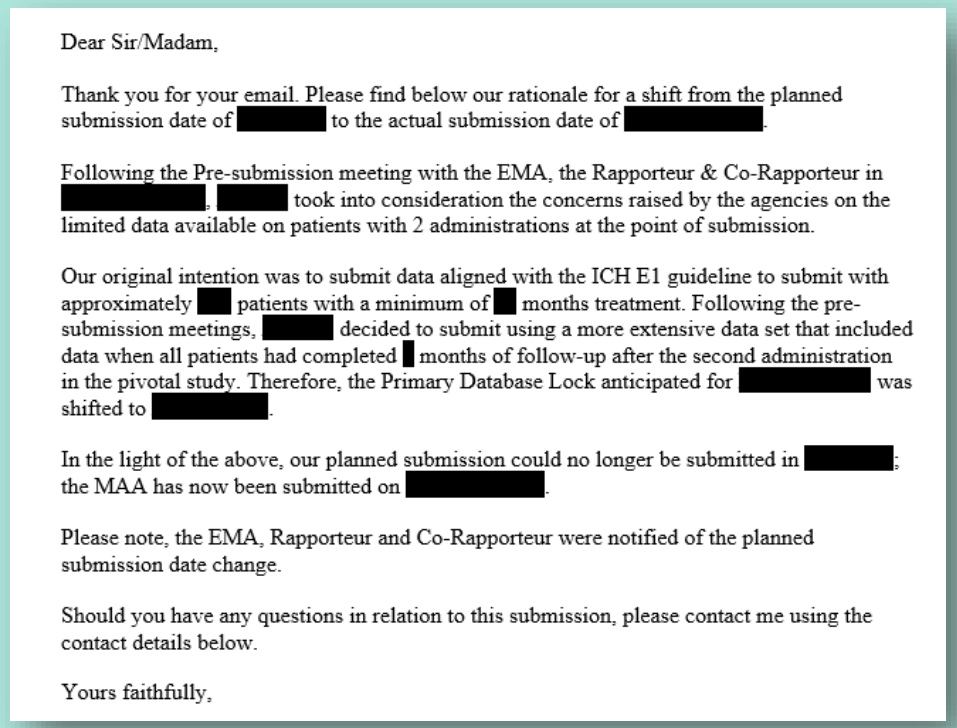
of the applicants **reacted to the automatic reminder** three month before planned submission

56%

of the applicants **did not provide justification** when modifying planned submission date

Example of justification given

Example of good communication practice



Dear Sir/Madam,

Thank you for your email. Please find below our rationale for a shift from the planned submission date of [redacted] to the actual submission date of [redacted].

Following the Pre-submission meeting with the EMA, the Rapporteur & Co-Rapporteur in [redacted], [redacted] took into consideration the concerns raised by the agencies on the limited data available on patients with 2 administrations at the point of submission.

Our original intention was to submit data aligned with the ICH E1 guideline to submit with approximately [redacted] patients with a minimum of [redacted] months treatment. Following the pre-submission meetings, [redacted] decided to submit using a more extensive data set that included data when all patients had completed [redacted] months of follow-up after the second administration in the pivotal study. Therefore, the Primary Database Lock anticipated for [redacted] was shifted to [redacted].

In the light of the above, our planned submission could no longer be submitted in [redacted]; the MAA has now been submitted on [redacted].

Please note, the EMA, Rapporteur and Co-Rapporteur were notified of the planned submission date change.

Should you have any questions in relation to this submission, please contact me using the contact details below.

Yours faithfully,

Example of poor communication practice

"following internal discussions there has been a change to the regulatory strategy"

"Bioequivalence study is not with the acceptance criteria"

"unforeseen delays in the development of the product"

"company and as such with limited resources at our disposal…potential acquisition consuming a lot of internal resources"

"internal reasons"

3

Case studies – examples of good & poor submission planning

Examples of good practices

ATMP classification

18/08/2015

Initial submission date is set for 1/7/19

Eligibility for centralized procedure

27/06/2022

Submission date is changed to 27/11/23

Letter of Intent (LoI) is received

11/04/2023

Submission date is left unchanged

Pre-submission meeting

16/08/2023

Submission date is left unchanged

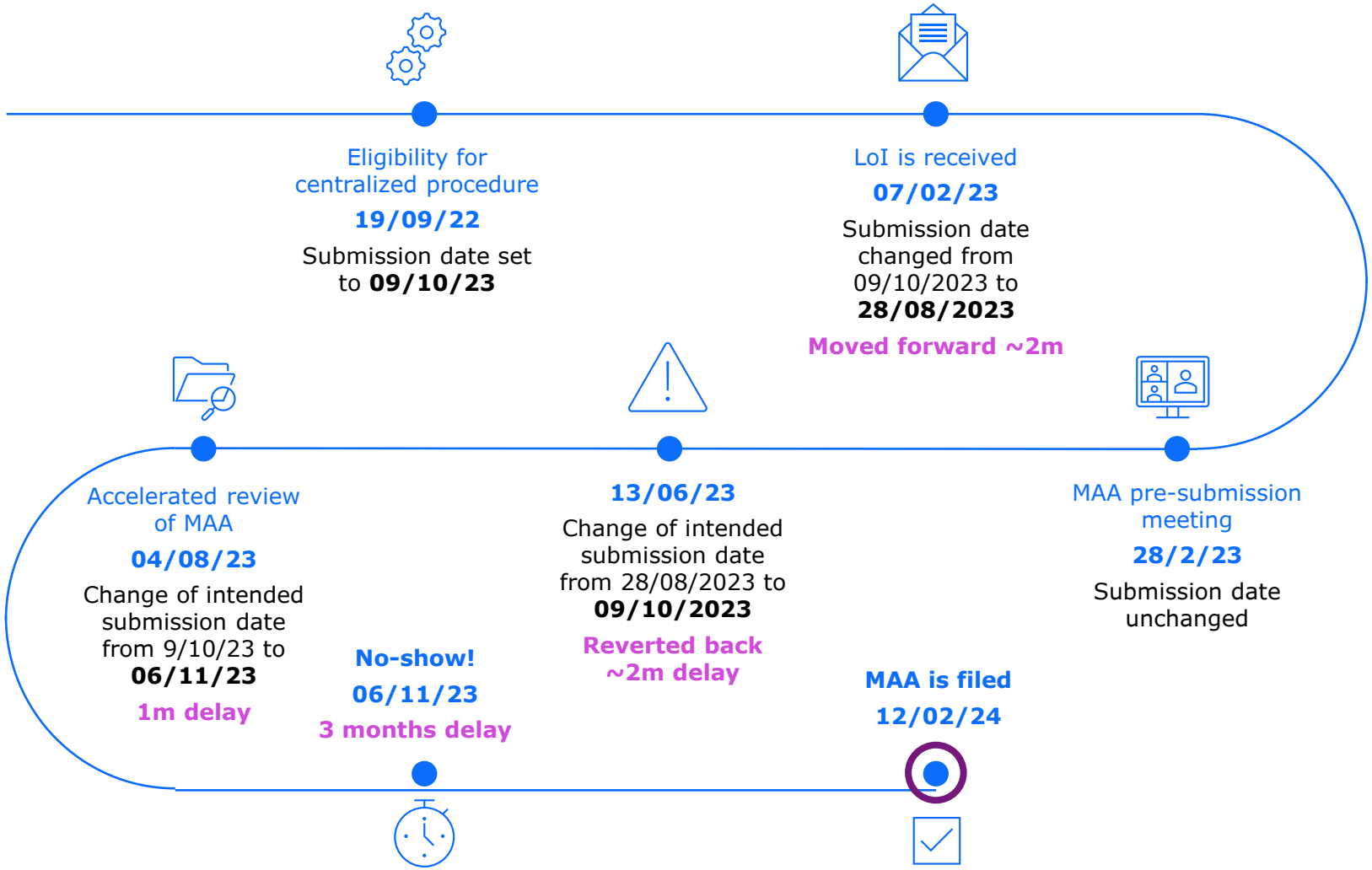
MAA is filed

21/11/2023

Initial submission date is set for 1/7/19

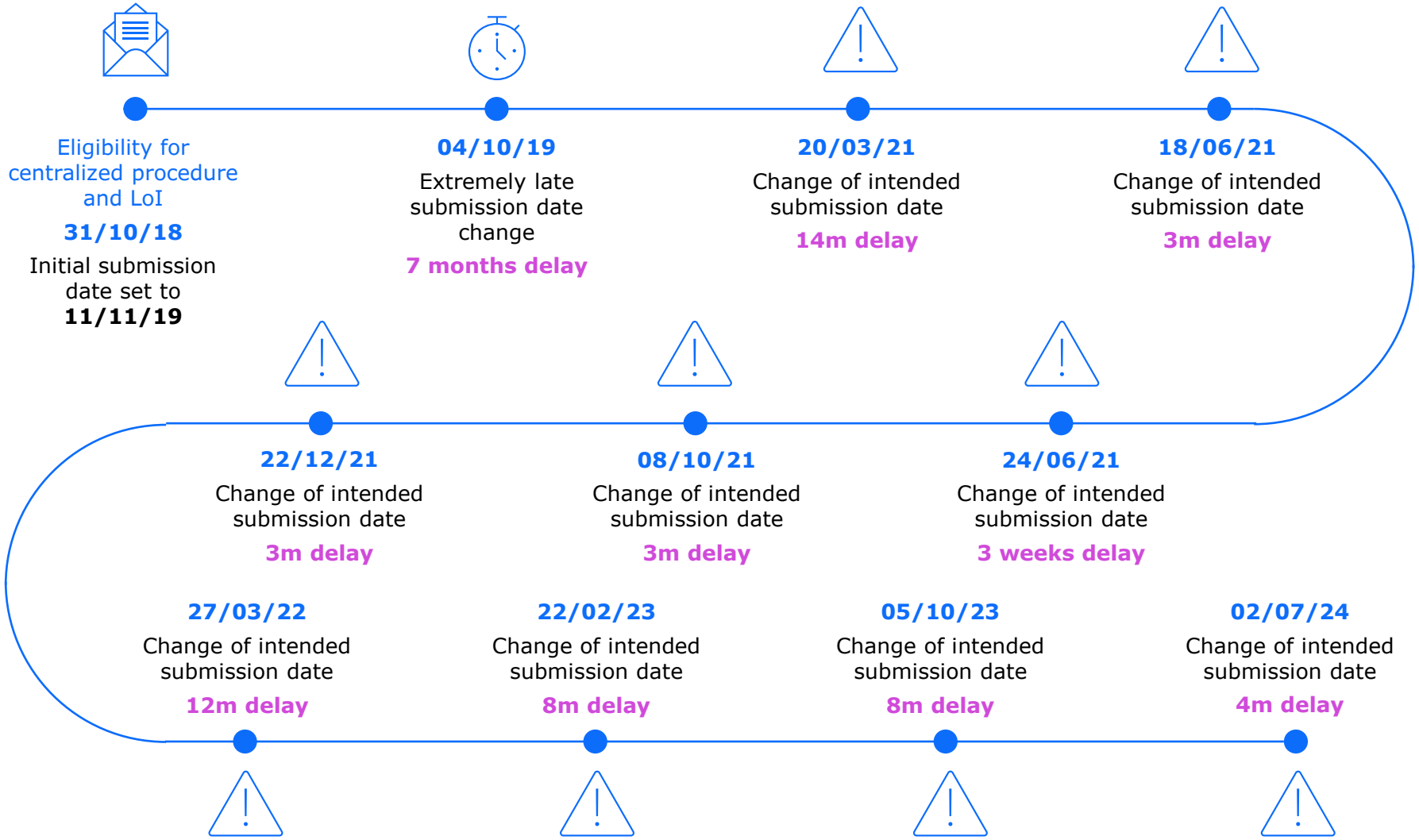
- LoI is delivered **within 1 year** of confirming eligibility
- **No delays** following the LoI
- **No major issues** during the pre-submission meeting
- MA submission is **finalized within 1 year** from the LoI

Examples of bad practices (1/2)



- Multiple delays following the LoI
- Multiple short-term delays in a single year (4)
- No-show - missing deadline
- Interactions extend into 2024

Examples of bad practices (2/2)



- Missing deadlines by one year
- All the delay following LoI
- Multiple delays in the same month
- More than 5 years in delays
- Still pending

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Thank you for your kind attention

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Best Practice approach using current guidance (human)

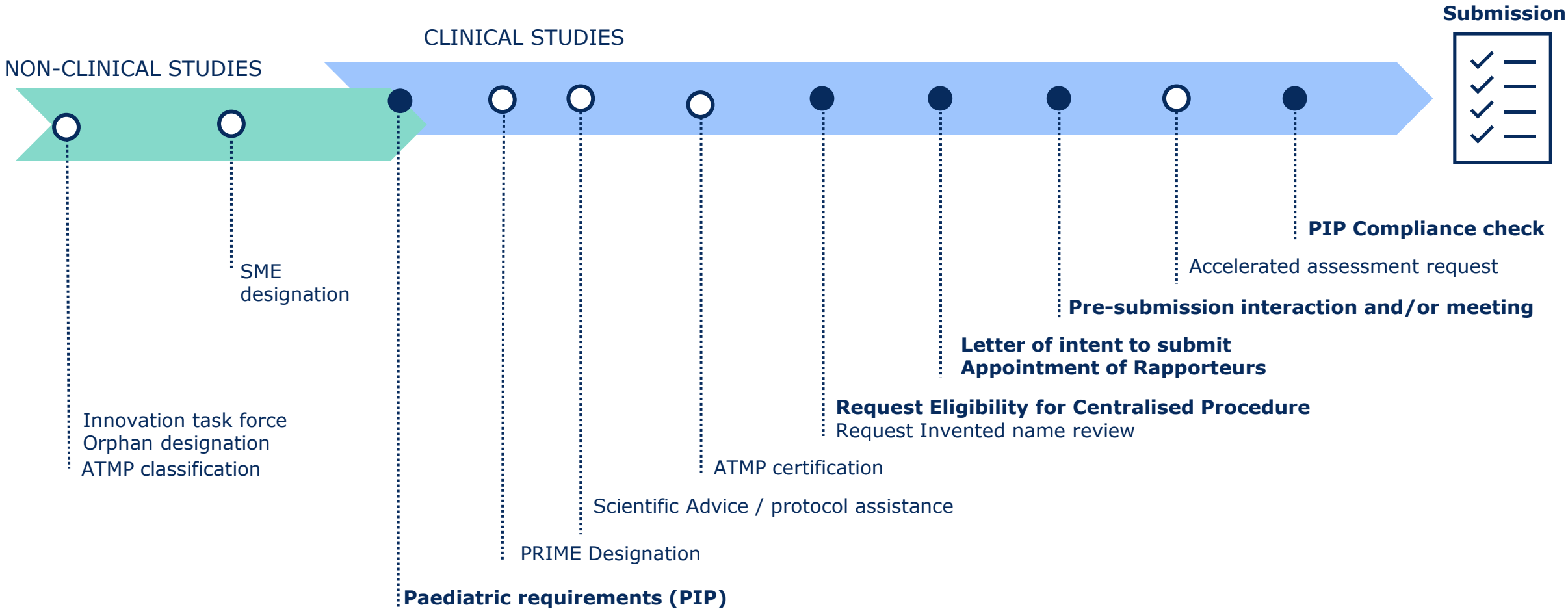
Jaime Oliva

Product Lead Therapeutic Areas Department

Scope of today’s session

- How to plan and submit a marketing authorisation application (MAA) – EMA perspective
- Reinforcement of communication – timepoints and mechanisms for notifying of delays, including a detailed justification
- Awareness of the guidance we have in place

How to plan and submit a MAA – EMA perspective



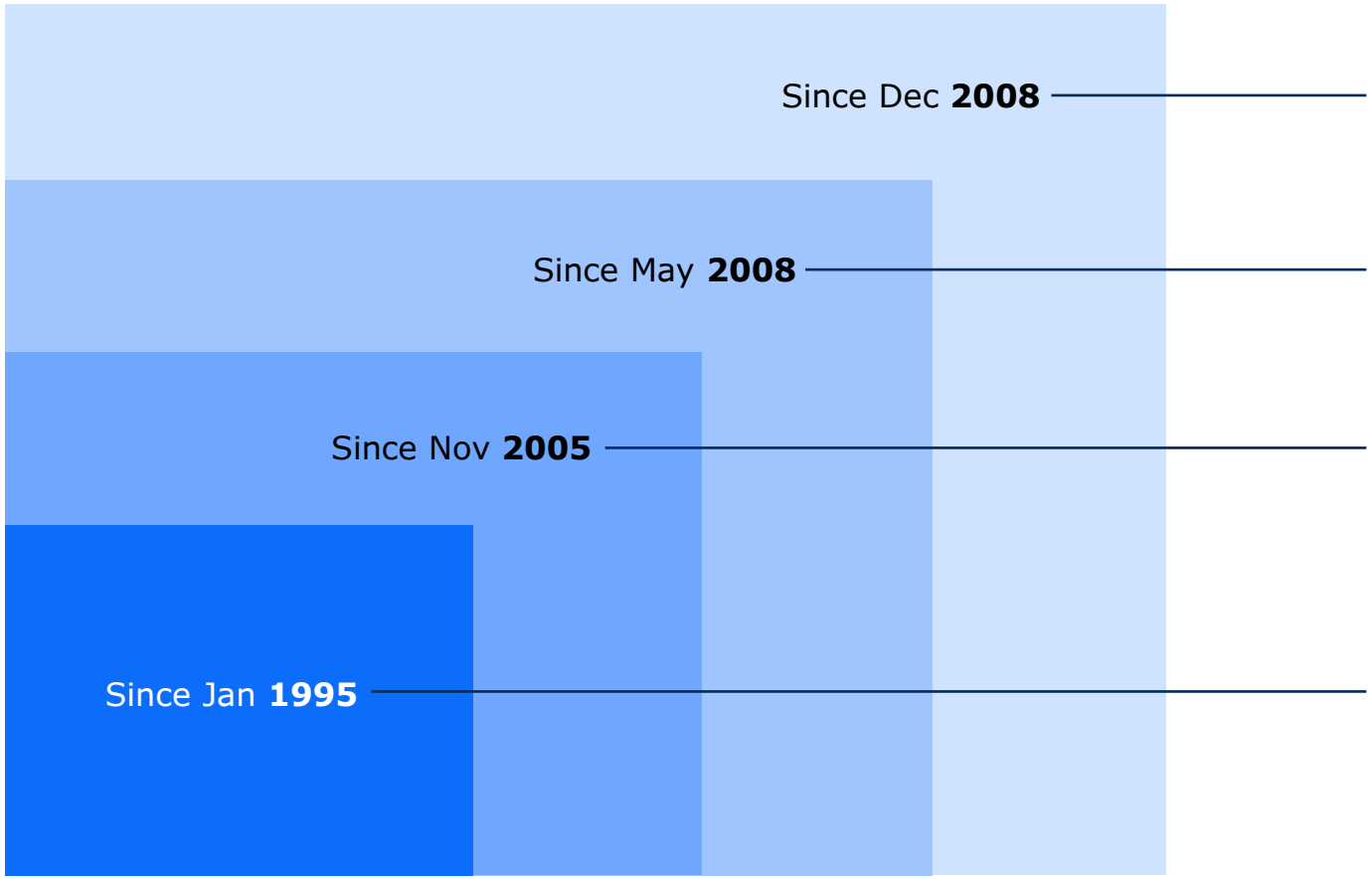
How to plan and submit a MAA – EMA perspective

1. Access to the centralised procedure (eligibility)

✓ **Mandatory scope**	Some products can only be authorised via the centralised procedure
✓ **Optional scope/automatic access**	Some products can be registered either via the centralised procedure or national procedures including MRP and DCP (choice of the applicant)
✗ **Optional/mandatory Scope**	Some products can only be authorised via national procedures

Centralised procedure - Eligibility criteria

Mandatory scope - Art. 3(1) Regulation (EC) No 726/2004



ATMPs (advanced theraphy medicinal products):
- Gene theraphy products
- Somatic cell therapy products
- Tissue engineered products

- Auto-immune diseases and other immune dysfunctions
- Viral diseases

- AIDS
- Cancer
- Neurodegenerative disorders
- Diabetes
- Orphan medicines

- Recombinant DNA technology
- Controlled gene expression
- Monoclonal AB

Centralised procedure - Eligibility criteria

Optional scope
Art. 3(2) Regulation (EC) No 726/2004

Art. 3(2)(a)	Art. 3(2)(b)
New Active Substances (as of 20 Nov 2005)	Known active substances Significant Innovation: therapeutic, scientific, and technical OR Interest of patients at community level

Automatic access
Art. 3(3) Regulation (EC) No 726/2004

Generics/hybrids/duplicate of a product authorised via CP

Paediatric medicines
Regulation (EC) No 1901/2006

MAA including paediatric indication in accordance with a PIP

OR

Paediatric Use Marketing Authorisation (PUMA)

Eligibility to the centralised procedure has **to be confirmed in advance** of submission of application: Pre-submission request form (Eligibility) with Annexes between 18 months and 7 months prior to the planned MAA submission date.

- Process takes 1 or 2 months
- Product Lead appointed

How to plan and submit a MAA – EMA perspective

2. Appointment of rapporteurs

- Rapporteurs **lead scientific evaluation** of the MAA – objective criteria, bidding
- Submit Pre-submission request form (intent to submit) with Annex - specify intended MAA submission date
- Ensure submission date is realistic and accurate – **resources on-hold!**
- Submit **7 months** before MAA; process takes at least one month

Reinforcement of communication – How?

- **Early dialogue** with the EMA, via pre-submission interactions (PSI) or pre-submission meetings (PSM), is encouraged.
- **Submit request** using the MAA PSI form
- **6 months** prior submission
- **Rapporteur** PSMs are also encouraged
- **Mature dossier** is expected
- Confirmation **3 months** before intended submission date – **critical!**
- **Inform changes** of the intended submission date as soon as possible using Pre-submission request form (notification of change)

Reinforcement of communication – Why?

Validation (examples of blocking issues)

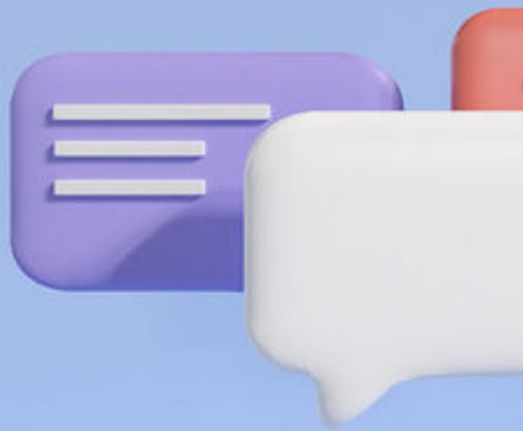
- **PIP compliance** and EMA decision needed – at least 2 months prior submission
- **Manufacturer** responsible for batch release in the EEA: missing/insufficient MIA*
- **Manufacturer** responsible for batch release in a third country
- **Batch control testing**: site located in 3rd countries NOT covered by an MRA**
- **Orphans**: EC decision on transfer not received (if orphan status wants to kept)
- **Generics, hybrids, biosimilars**: reference product is under data/market exclusivity
- **Duplicates**: missing EC letter

*MIA: manufacturing or importation authorisation
**MRA: mutual recognition agreement

Reinforcement of communication – Why?

Evaluation (non-acceleration)

- MA assessment takes **up to 210 active days**.
- **Two clock-stops** occur for applicant responses: at D120 (LoQ) and D180 (LoOI).
- Clock-stop duration **depends on applicant response time**, CHMP approval.
- **No new study data** should be introduced in the responses, unless requested.
- **Respond** LoQs within 3 months and LoOI within 1 month
  - Extension may be possible **duly justified** – clock-stop extension request form



⚠ **Immature dossier** will impact expected timelines and workload

Reinforcement of communication – take home messages

- ✓ Submission dates should be **realistic**, not overly optimistic.
- ✓ Confirm submission dates **3 months** before intended submission.
- ✓ Engage in **early dialogue** with EMA/Rapporteurs during pre-submission.
- ✓ **Data** must fully support dossier requirements or prior discussions.
- ✓ Notify EMA immediately if **submission delays** occur.
- ✓ **Discuss with EMA** if intended submission date isn't met.
- ✓ Failure to communicate delays may require **procedural timetable adjustments**.

Awareness of the guidance we have in place (references)

- Pre-authorisation guidance | European Medicines Agency (EMA) (europa.eu)
- Questions and answers on the procedure of PIP compliance verification at EMA, and on paediatric rewards (europa.eu)
- Microsoft Word - FINAL Revision December 2008 - Time allowed to Aplicants to Answer LoQ-LoOIs .doc (europa.eu)
- Best practice guide on timing and planning of submission applications.

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Thank you for your kind attention

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