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Industry representatives' viewpoints on submission predictability

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Industry Views

Lack of predictability in submissions impacts EU Network resources and patient access to medicines.

Industry is dedicated to enhancing submission predictability and fostering better communication with EMA/Raps.

Industry is committed to defining the intended submission date with care and following EMA/HMA Best practice guide and to provide accurate information on the LoI and its annex & follow the Pre-authorisation guidance | European Medicines Agency (EMA) (europa.eu)

Where does Industry submit their MAAs?

Global Registrations: 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)

Critical role for EMA: Some global Regulators rely on EU's regulatory authorization decisions

Business case underpins launch: Global filing plans are drawn up taking into consideration commercial and access perspectives

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Challenges of Global Submissions – Planning

Stakeholder communication on planned submission timelines

Varying advance notification requirements from different regulators

- US - FDA – Voluntary: No advance notification required
- Japan – PMDA/MHLW – Voluntary: 3 months in advance
- China – NMPA – Voluntary: No advance notification required
- Australia - TGA – Required: 15 days - 1 month in advance plus annual pipeline meetings
- Switzerland – SwissMedic – Voluntary: 4-6 months in advance
- Canada – Health Canada – Voluntary: Planned submissions forecast – supplied every 6 months
- UK - MHRA - Required: 7 months in advance
- EU – EMA – Required: 7 months in advance - with monthly deadlines for submission

Predicting Our Submission Dates: 100% success is not realistic

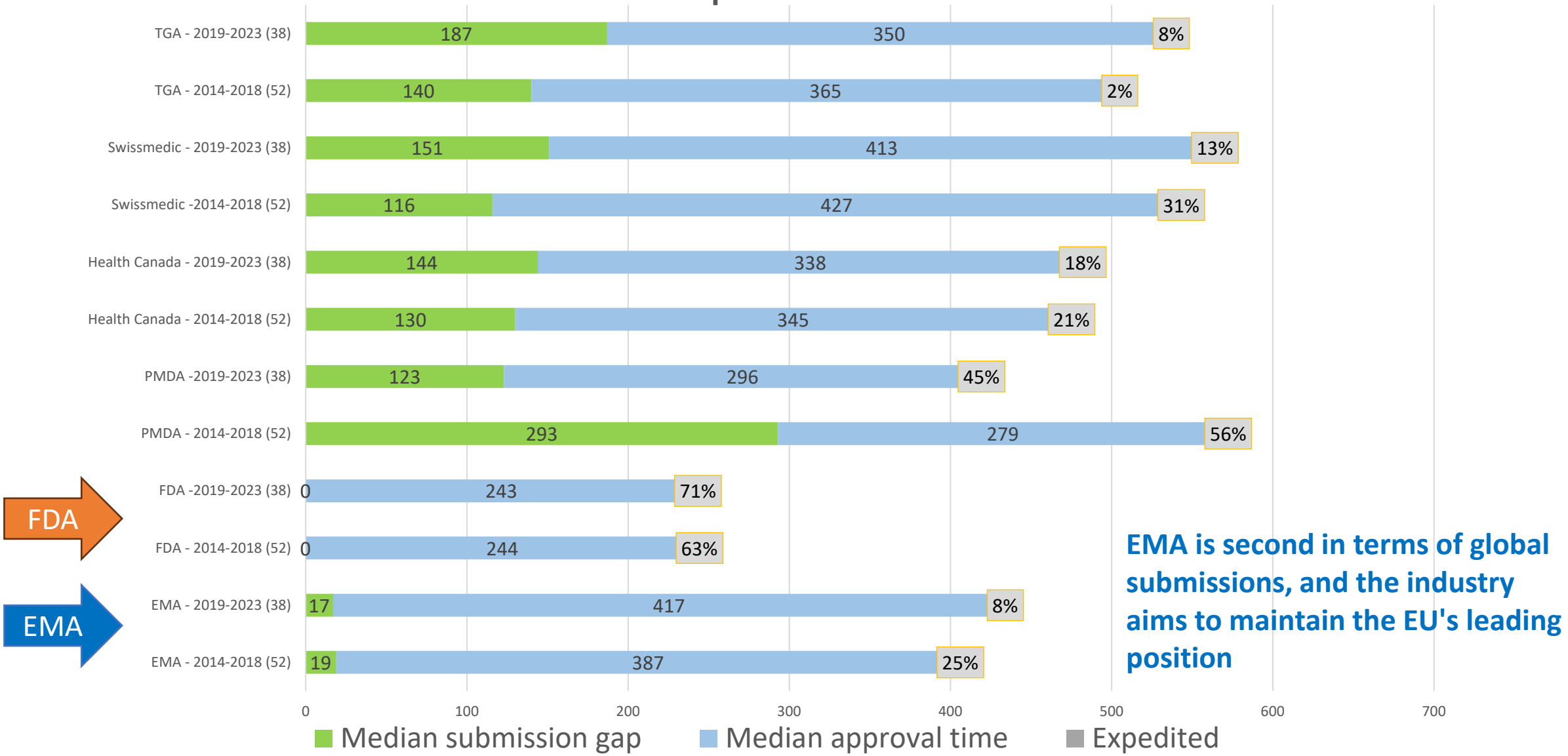
Considerations when developing a Global Submission plan

- Understanding the complexity of different regulatory requirements, pharmacopeia monographs, guidelines, legislations, diagnostics and devices requirements.
- Requirement for local clinical trials - local patient data requirements
- Addressing divergent Advice or agency interactions from different regions or countries
- Understand the different regulatory pathways available, including differences in timing for the assessment of the MAA
- Different regulators perspectives concerning regulatory requirements for submission (data maturity)
- Availability of Expedited Pathways
- Access to early regulatory interactions during drug development (e.g. Scientific Advice options, Breakthrough; PRIME; SENKU)

Challenges that may impact planned Submissions

- Potential Impact of Global Submissions Resulting from Prioritization of Global work-sharing initiatives e.g. Project Orbis; Access consortium; OPEN
- Availability of company resources & need to prioritise some submissions
- Incorporate HTA advise in submissions
- Need to adapt the dossier content to address specific countries or regions requirements
- The competitive landscape impacts the drive for a possible early submission.
- Late response(s) from regulators on critical topics impacting future submissions
- All these challenges may impact EMA submissions

Planning Submissions Among Regulators - Approvals timelines – CIRS Report - 2024[1]



EMA is second in terms of global submissions, and the industry aims to maintain the EU's leading position

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.

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What are the main reasons submission dates can change?

- Uncertainty of the clinical trials outcome - Failed or need to extend clinical studies
- Additional or revised Statistics Analysis Plan after input of experts
- Impact of multi-regional clinical trials in global submissions
- Uncertainty on duration of patient recruitment, especially for rare diseases
- Complexity of the regulatory environment
- Additional requests from Regulators at pre-submission interactions (e.g. regulator can request additional studies before submission)
- Unforeseen GMP and GCP issues – Data integrity
- Commercial reasons – mergers & acquisitions, company resourcing
- Time to event based endpoints, where time to event is longer or shorter than expected based on prior data
- Unforeseen issues with third parties:
  - ASMF – Manufacture of the active substance
  - Manufacture of excipients
  - External support

Conclusion

Industry is strongly committed to improving submission predictability

Industry is committed to follow EMA/HMA Best practice guide / pre-authorisation guidance and to provide accurate information on the Letter of Intent and its annex

Submission predictability is a priority on trade associations' agendas

100% success is not realistic

Enhance Earlier Dialogue - Regulators support and earlier interactions will enhance the likelihood of submission predictability

Positive clinical trials outcomes are pivotal for submissions and complete dossiers

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Case studies: Innovators, Generics and Biosimilars

Stefan Schwoch (EFPIA), Alexandra Oger (EFPIA), Rebecca Lumsden (Vaccines Europe), Andrew Modley (Medicines Europe)

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Innovator case study 1: New MAA: Oncology product for breast cancer

Stefan Schwoch, PhD
Vice President, Regulatory Leader-EMEA, Eli Lilly and Company
EFPIA

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Submission Planning: Starting Principles

Focus on being as expedient as possible to benefit patients, which can result in justified reasons to adjust global submission timelines

Growing complexity of global medicine development plans and inherently in modern medicines (e.g., diagnostics, devices) necessitates level of flexibility

Imperative to communicate timely and clearly with EMA, Rapporteur teams, and global regulators whenever changes are necessary

Many regulators across the world rely upon EU authorisation decisions so achieving optimal EU timelines have a global impact

Submission Planning: Oncology product for breast cancer

Nov 2015

Notified EMA of Apr 2016 MAA submission plan; A

Jan 2016

Updated EMA/Rapps – no official change to a new date – that Apr submission dependent on event-driven Ph2 interim study will come later; Strategic decision needed whether to also include interim data from a further Ph3. To confirm date in Feb/Mar

Mar 2016

Communicated to EMA/Rapps that we'll submit w/ results from both studies; submission will not be before Oct 2016 (to confirm date in Jun/Jul)

Jun 2016

Submission of revised LoI noting submission now planned for Dec 2016; date B

Aug 2016

Communicated to EMA/Rapps that DMC recommended continuing event-driven study; next update planned for 2Q2017 with a revised LoI

Sept 2016

Official change of planned submission date to July 2017, C; also, indicated change of pharmaceutical form / presentation

Jul 2017

Submitted MAA based on 1 Ph2 and 2 Ph3 studies

Jul 2018

Received positive CHMP opinion

Overall 3 submission dates communicated: initial and 2 changes: A. B. C

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Submission Planning: Lessons Learned

Illustrated complex development plan where event-driven study design impacted anticipated submission timing and required flexibility; In addition, there were also strategic changes regarding which studies to include

Europe should facilitate competitive review timelines (e.g., opportunity to submit on any day each month) since EU submission timelines impact international submissions and approvals

Intent to submit in EU at the same time as US and other major markets around the world

While industry can continue to improve submission planning and communications, some flexibility can ultimately benefit patients

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Innovator case study 2

Alexandra Oger
EFPIA

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Background information

PRODUCT	• Product X intended to treat disease with high unmet need as no systemic treatments currently exist
MOA	• New mechanism of action (first in class product)
FILING STRATEGY	• Global filings planned in major markets (including US NDA and EU MAA)
CLINICAL STUDIES	• Phase 2 single arm trial (SAT) evaluating product X in indication A • Phase 3 study evaluating product X in indication B with pre-specified interim & final analyses (IA1, IA2 and FA)

NDA: New Drug Application; MAA: Marketing Autorisation Application

Regulatory agency interactions

FDA meeting

FDA concluded that filing based on Single Arm Trial (SAT) would be acceptable to support NDA approval in the proposed indication A

→ Company decision to file with results from SAT in the US*

CHMP SA

CHMP concluded that filing only based on a SAT would be very challenging and that a randomised clinical trial would be desirable to support the MAA in the proposed indication A

→ Company decision to combine indications A & B in the EU:

1. Phase 3 data in a second indication would support the safety of the product;
2. While postponing the submission, additional data from the SAT would be available at the time of filing

*and 13 additional countries for indication A

Pre-submission interactions with EMA

Month-Year	Communication w/EMA	Content (Reason for delay as communicated to EMA)	Delay (months)
Jun-Y	**LoI-1** submitted 7 months prior to planned MAA filing date (Feb-Y+1)	-	-
Sep-Y	**LoI-2** with updated MAA filing date (Apr-Y+1)	**Reason**: Date postponed due to delay in the availability of the study results *(due to delay in event-driven analysis - Ph3 IA1)*	3 months
Nov-Y	**LoI-3** with updated MAA filing date (May-Y+1)	**Reason**: Additional delay due to internal reasons → Below additional details were not communicated to EMA: • CHMP asked for a randomised study to support indication A which was not performed • There were additional complexities due to CHMP Scientific Advice feedback that resulted in more time needed to build the MAA dossier and author CTD modules (vs supplemental NDA for US submission)	1 month

LoI: Letter of Intent

Pre-submission interactions with EMA

Month-Year	Communication w/EMA	Content (Reason for delay as communicated to EMA)	Delay (months)
Dec-Y & Feb-Y+1	2 successive emails from EMA requesting confirmation of MAA filing date (targeted in May)	No immediate response was given by the Company as internal discussions were ongoing in a very select group of unblinded people. Details were not to be shared externally	-
Mar-Y+1	Company update via email	**Reason**: read-out of one of the pivotal studies postponed to the next interim analysis due to immature data. New filing date still under discussion → It took some time to respond as IA1 results from Ph3 were awaited to make any decision to file in the EU: • either based on IA1 data or • wait for more mature IA2 data considering global filings (new CSR to be developed) & market access implications	-

Pre-submission interactions with EMA

Month-Year	Communication w/EMA	Content (Reason for delay as communicated to EMA)	Delay (months)
Apr-Y+1	**LoI-4** with updated MAA filing date (Nov-Y+1)	**Reason**: delay because filing will be based on next interim analysis → LoI was submitted once internal decision was made on the revised filing date based on Ph3 IA2 data	6 months
Aug-Y+1	Company update via email	Communication to EMA/(co)-Rapporteurs with the Ph3 IA2 results for indication B	-
Aug-Y+1	Email from EMA requesting confirmation of MAA filing date (targeted in Nov)	Company response confirming the November filing date and indicating that the pre-submission interactions form and annexes (including Briefing document) would be submitted in September	-

→ MAA was ultimately submitted in November - as confirmed to EMA 3 months in advance

Key take aways

Lessons Learned

- EMA pre-authorisation guidance could not be strictly followed despite Company intent to communicate timely to EMA about any change in submission date
- Reason provided to EMA could not always be sustantiated due to internal strategic discussion and additional time required for change in submission strategy/data package which led to delays
- Very straightforward exchanges with the EMA and receipt of automatic reminders to confirm planned submission date

Best Practices

- Define intended MAA submission date **with careful consideration** to be realistic and accurate and avoid multiple delays
- Include necessary information related to the intended MAA in the **Letter of intent and its annex** as it will help identifying potential challenges such as projected DBL dates for pivotal clinical studies

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Changing submission dates: Best Practices & Innovator case study 3

Rebecca Lumsden, PhD
Vaccines Europe

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What can trigger changes in submission dates?

“The best laid schemes o’ mice an’ men / Gang aft agley,”
Robert Burns

Translation “The best laid plans of mice and men, often go awry”

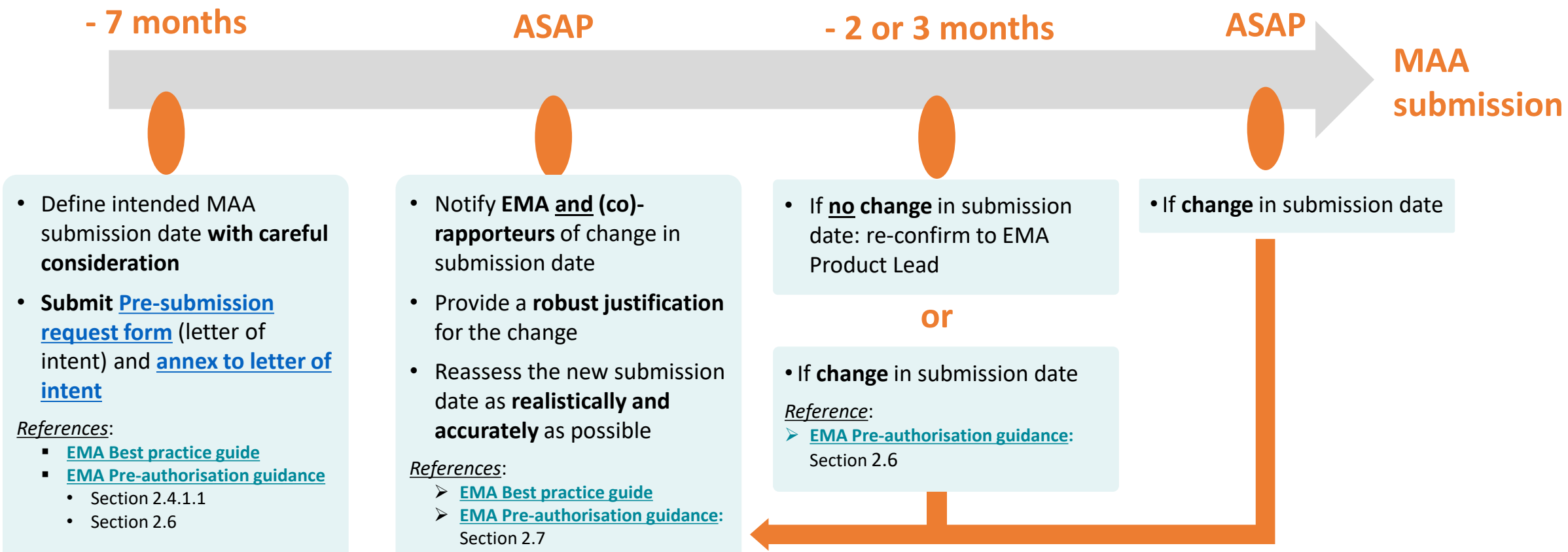
Pivotal study fails
The sponsor informs EMA and Rapporteurs of withdrawal of planned submission after a pre-planned interim analysis fails.

Pivotal study results not clear-cut
The sponsor requires additional time for re- or additional analysis, re-evaluation of the statistical plan and submission strategy.
More interactions with Health Authorities including Rapporteur teams are needed - impacting planned submission timelines.

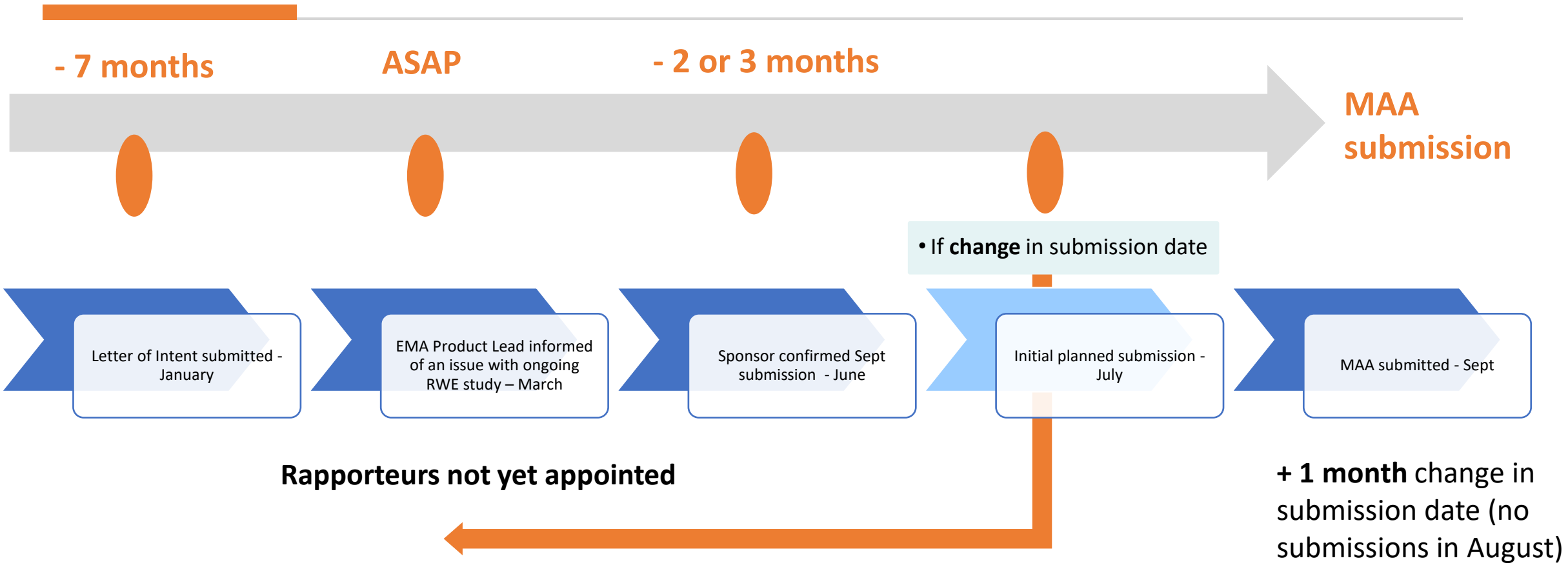
Data integrity issues
Internal audit/whistle-blower generates concern with dossier data after Letter of Intent issued – company delays submission to investigate
Cyberattack – data requires review for validation purposes - company delays submission to investigate

EMA submission follows first-global approval
Dossiers developed initially for a single regulator (no global strategy in development) unlikely to meet EMA requirements without changes e.g. additional studies, re-formatting, translations

Summary of EMA guidance to improve submission predictability



Following best practice - Case study 3: unanticipated change to new MAA planned submission



Top 5 Best Communication Practices to be implemented

1. Define intended MAA submission date with careful consideration in Letter of intent	Plan submission date **as realistically and accurately** as possible to avoid future changes
	Information provided in Letter of intent and its annex is crucial for EMA, Rapporteurs, and Assessors to allocate their workload efficiently; it identifies potential evaluation challenges and facilitates rapporteurs bidding process and better resources/expertise allocation
2. Notify EMA timely of any change in intended submission date or cancellation and provide reason for such change	Change should be substantiated by **robust justification** *(can be linked to aspects covered in the Annex to Letter of intent)*
	Alternative date should be based on **realistic and accurate** timing to avoid future changes
	Follow the **EMA Pre-authorisation guidance**[1] to inform both EMA and the (co-)rapporteurs
	From Jan 2025, changes to the intended submission date > 60 days will incur a EUR 4200 fee.

1. **LINK:** https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/european-medicines-agency-pre-authorisation-procedural-advice-users-centralised-procedure_en.pdf

Top 5 Best Communication Practices to be implemented

3. **Promptly reply to EMA**	Automatic reminders sent 3 months prior to initially communicated MAA submission date (Letter of intent) → to confirm date & allocated resources
	EMA plans to expand this project to major planned post-authorization submissions: it will be critical for Industry to respond adequately when requested
4. **Formally nominate a contact person and ensure change in contact person is communicated without any delay to EMA**	Avoids any communication risk with EMA on planned MAA submission

5. **Follow the EMA Best practice guide**[1]

1. **LINK:** https://www.ema.europa.eu/system/files/documents/regulatory-procedural-guideline/wc500239906_en.pdf

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Generics and Biosimilars

Andrew Modley
Medicines for Europe

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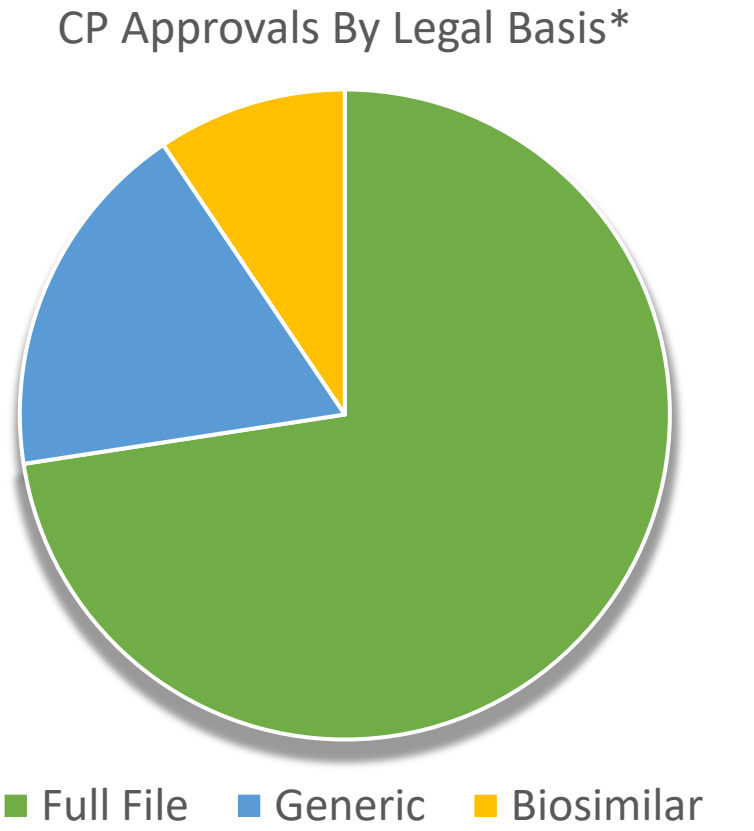
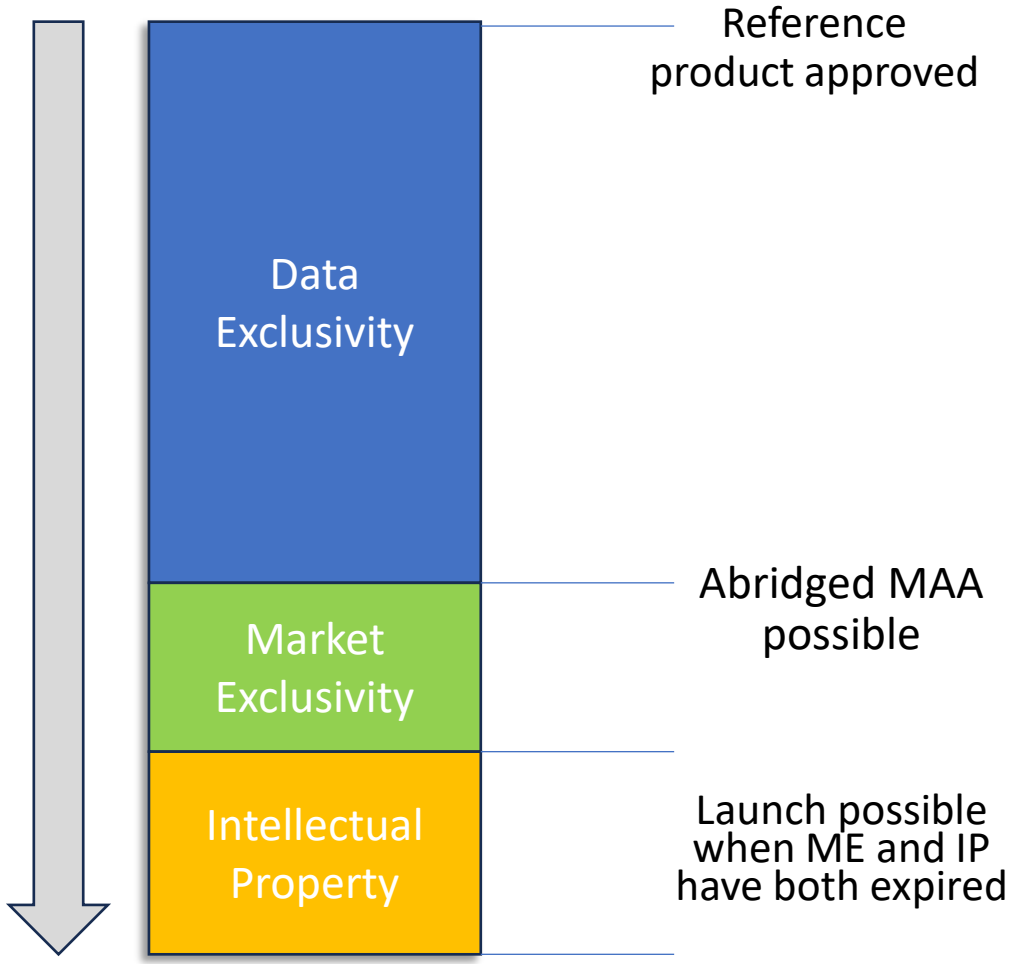
Abridged Applications and the CP

- Mandatory for biosimilars (technology falls within compulsory scope)
- Optional for generics IF reference product was approved via the CP
- Decentralised Procedure accounts for majority of generic submissions



*Community Authorisations granted 2020 to 2023 based on data published on EMA website (accessed 2nd September 2024)
**CMDh statistics – 2023 - link

Determining Target Submission Dates



- Goal for generics/biosimilars is to launch in the first wave.
- Target submission date is determined by counting backwards from planned launch date to accommodate sufficient time for:
  - Regulatory approval
  - Pricing and reimbursement
  - Launch critical variations
  - Scale-up and launch activities

But it takes some time after innovator/approval and launch to establish a business case…

Need to Build a Business Case First…

- Must be selective (can't develop everything!)
- Monitor how innovator market develops
- Predict future direction of innovator market
- Develop assumptions about potential competition (other innovators and other follow-on medicines)
- In-licensing/out-licensing/partnerships
- Risk tolerance
- Cost of goods/margins
- Review regularly and adapt to changes

Goal is to achieve best possible compromise between a robust business and sufficient time to hit first wave launches

For global developments the European business case may be less critical

Key Influences of Development Timelines

- API availability and source selection
- Device availability (if required)
- Development complexity and risks
- Evolving IP landscape
- Investment in new/necessary technologies
- CMO/partner availability
- CRO availability (esp biosimilars)
- Resource and budget considerations
- Building in adequate contingency
- Ensuring submission that batches are within shelf-life during assessment
- Potential for new guidance, monographs etc that impact on supporting data requirements

Development timelines for follow-on medicines are influenced by many factors (not just innovator approval dates)

The Final Months Before Submission

Developments timelines are dynamic and frequently change. HOWEVER, delays to agreed CP submission dates would generally be driven by significant and unexpected challenges in the final 7-9 months prior to submission.

- Manufacture/testing/characterisation of submission batches
- Scale-up and commercial scale process validation (non-standard process)
- BE study batch selection and in vitro data to support biowaiver (generics)
- Initiation of stability studies and generation of 6 months of stability data
- Completion of BE study (if required), bioanalytical work, clinical study report
- Phase III CSR and conclusion of in vitro work to show biosimilarity (biosimilars)
- Completion of dossier compilation, final review and remedial action
- Publishing and submission

Potential Delays to Agreed Submission Date

- Time to address recommendations from pre-submission meeting (esp biosimilars)
- Unexpected problems manufacturing/characterising submission batches
- Delays in initiation of the bioequivalence study (e.g. importation/reference product availability)
- Bioequivalence study failure/bioanalytical method issues
- Delays concluding PIII CSR (biosimilars)
- Stability failures
- Testing delays at final stability timepoint
- Remediation of critical gaps during final review
- Out of specification results triggering internal investigation
- Changes in regulatory or commercial strategy

Optimising Submission Predictability

- Be realistic with submission dates based on availability of supporting data
- Submit a letter of intent!
- Build in adequate contingency time for remediation at the end of developments
- Inform EMA promptly in case of delays to submission with clear rationale
- Ensure that internal SOPs and work instructions reflect the importance of realistic planning and good communication with EMA
- Ensure that adequate training is in place on use of the CP
- Monitor the external environment for changes to processes
- Inform EMA if internal contacts change