EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Parallel Scientific Advice 101

FDA-EMA Parallel Scientific Advice (PSA) Program

Presented by Anabela Marcal on 16 March 2022
EMA Liaison Official to FDA

Webinar Objectives

- Provide an overview of the Parallel Scientific Advice (PSA) program. Participants will gain a general understanding including how to submit a PSA request, the expected procedure timeline, and outcomes.
- Examine findings from a 5-year PSA program review and gain insights into the PSA process by reviewing case studies.
- Understand best practice recommendations for those considering a PSA request.

PSA 101 - Agenda

- What is Parallel Scientific Advice (PSA)
- Overview of EMA-FDA collaboration
- PSA Method
- Sponsor submission to the Agencies

What is PSA

A mechanism where EMA and FDA concurrently exchange their views on scientific issues with the sponsor

- Increase dialogue early in product lifecycle
- Deepen understanding of regulatory decisions
- Optimize development
- Avoid unnecessary testing

Conducted under Confidentiality Commitments

The best candidates for PSA

- important medicinal products (unmet medical needs)
- indications lacking development guidelines, or significantly different guidelines

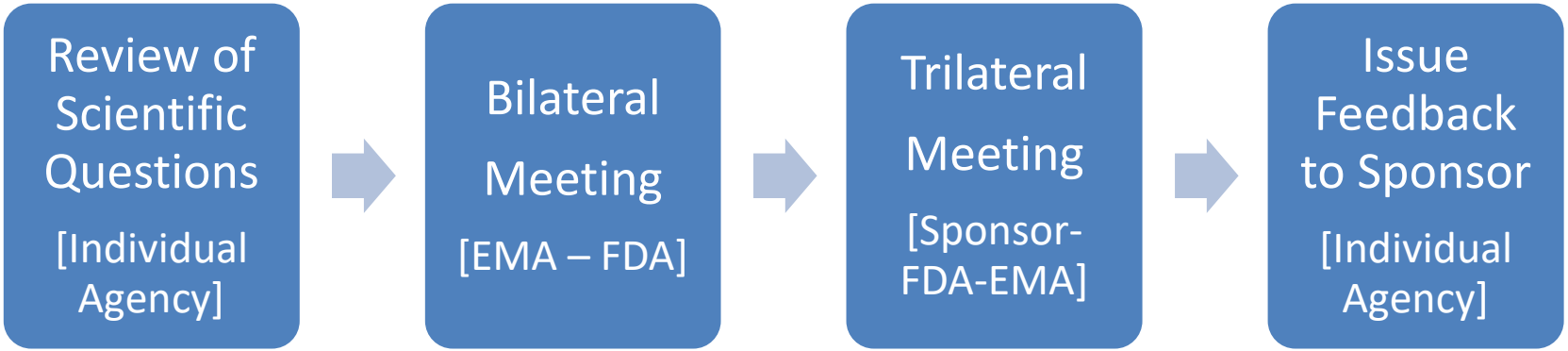
PSA

- **Voluntary,** at request of sponsor
- Questions on product development put both to EMA and FDA
- Scientific advice can be provided on **any scientific question**
- Advice can be asked only for a specific part of the development
- Discussions between EMA-FDA, and joint discussion with sponsor
- Agencies issue own responses to sponsor’s questions in line with usual procedures

Will a PSA request be granted?

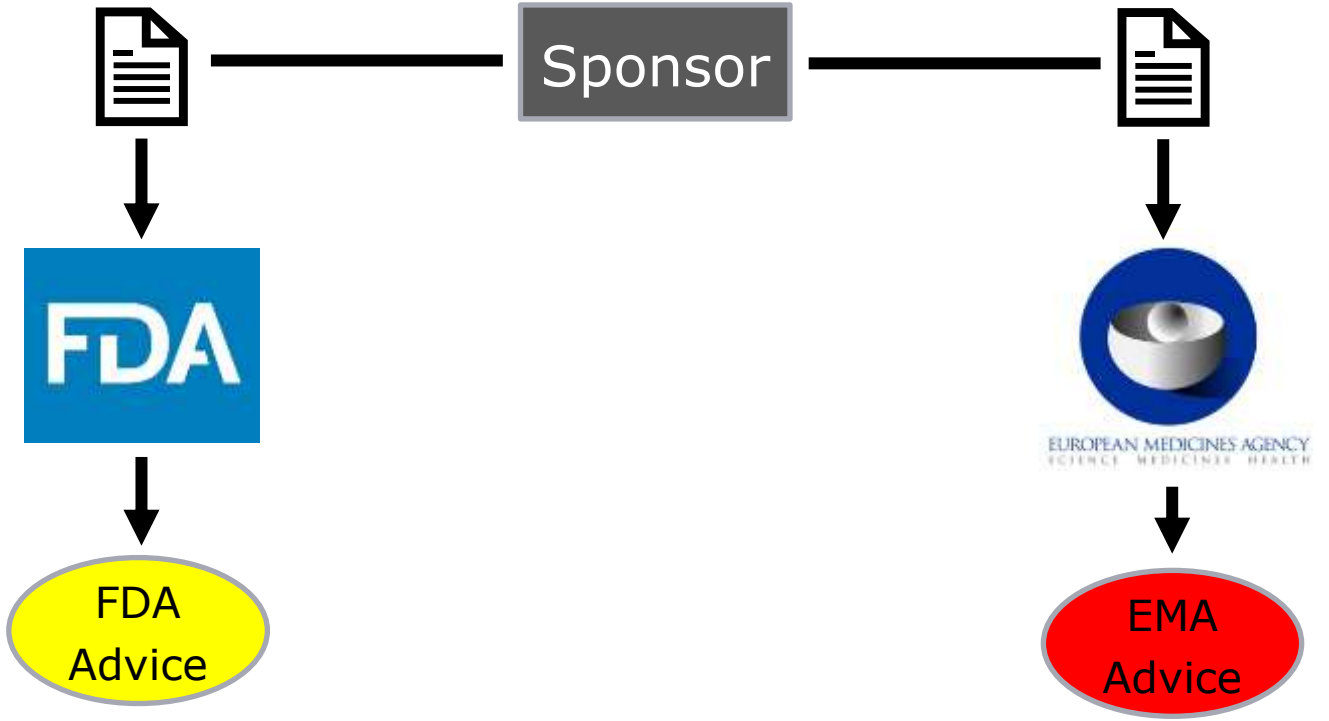
- A PSA request does not guarantee the PSA procedure will be granted
- For various reasons, one or both agencies may decline to participate in such a procedure
- If request not granted:
  - Sponsor can still pursue a Scientific Advice (SA) procedure with each Agency individually
  - Or consultative advice *(experts from one Agency will be invited to participate in the discussions of the other)*

Overview of Collaboration

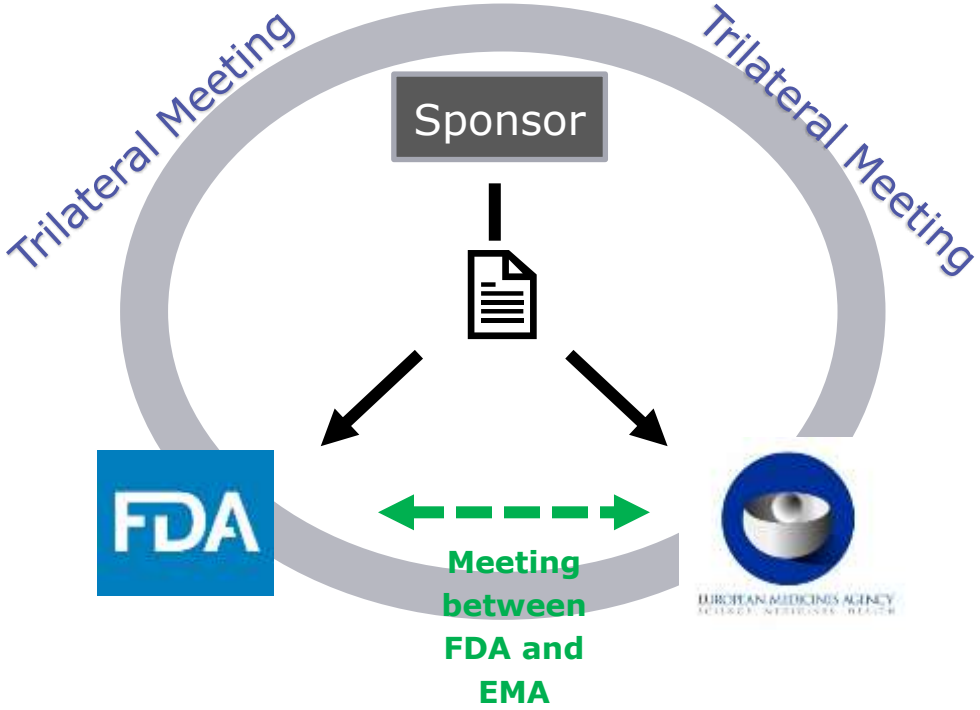


The overall process for PSA is aligned with CHMP Scientific Advice (SA) procedure and timeline for Type B Meeting at FDA

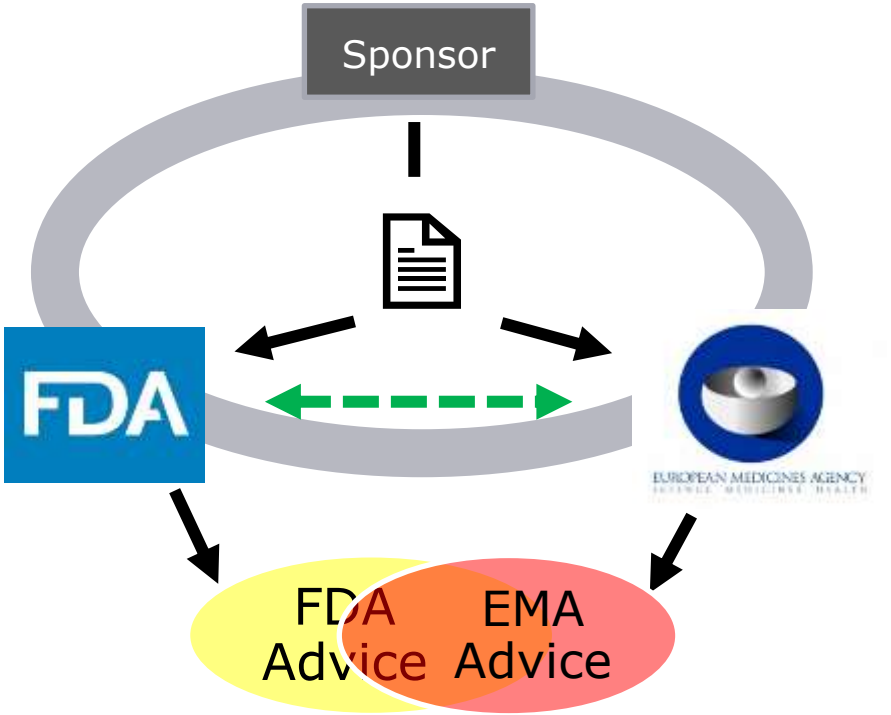
Standard Method for Scientific Advice



PSA Method



PSA Method



What gets submitted to the Agencies?

PSA Request

Meeting Package

Information Requests

Trilateral Presentation

Meeting Minutes

- the product in development
- why a discussion with both FDA and EMA would be beneficial
- specific questions requiring clarification
- desired goals for the meeting
- explicit authorization for the agencies' comprehensive exchange of all information relevant to the product

A single "Request for PSA" letter sent to both FDA and EMA

- Email: emainternational@ema.europa.eu
- Email: US-FDA-EUR@fda.hhs.gov

Why PSA?

- Opportunity for engagement with both regulatory agencies
- Avoid duplication of work
- Common approach where feasible or better understanding of the reasons for potentially remaining divergences

  'Both agencies will strive to provide PSA responses that are convergent' (PSA General Principles)

- Opportunity to simultaneously solicit and receive "official" feedback

Resource for Applying for PSA

General Principles for PSA document:

https://www.fda.gov/media/105211/download

https://www.ema.europa.eu/en/documents/other/general-principles-european-medicines-agency-food-drug-administration-parallel-scientific-advice_en.pdf

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July 2021

GENERAL PRINCIPLES
EMA-FDA PARALLEL SCIENTIFIC ADVICE
(HUMAN MEDICINAL PRODUCTS)

The European Medicines Agency (EMA) and the U.S. Food and Drug Administration (FDA) of the U.S. Department of Health and Human Services have a program to provide parallel scientific advice (PSA) to sponsors. The goal of the PSA program is to provide a mechanism for EMA assessors and FDA reviewers to concurrently exchange with sponsors their views on scientific issues during the development phase of new medicinal products (i.e., new human drugs and biologics). Such interactions are expected to increase dialogue between the two

Further information

Anabela.marcal@ema.europa.eu
emainternational@ema.europa.eu

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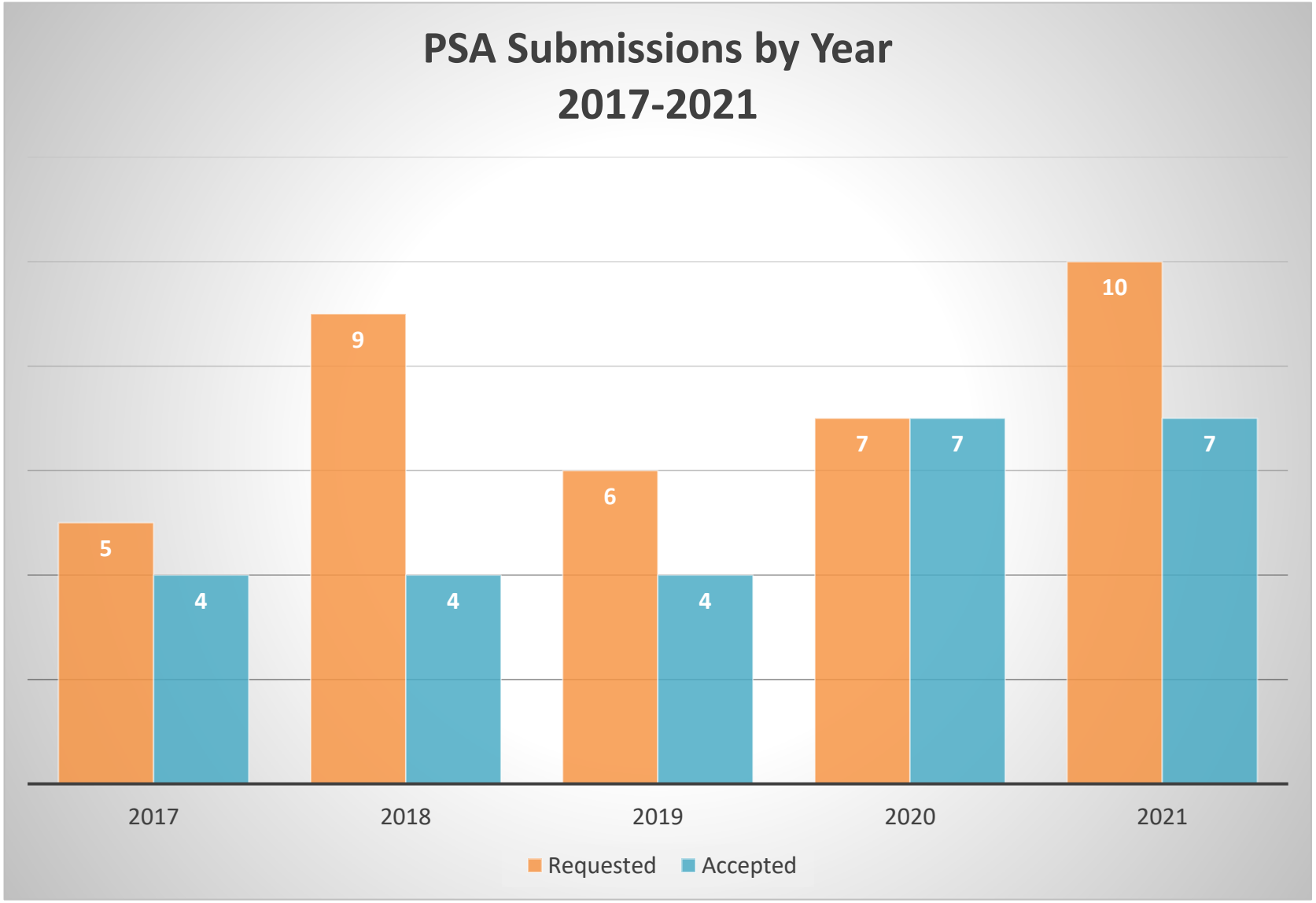
5-Year Program Review and "Myth-busting" the PSA Timeline

LCDR Shannon Thor, PharmD, MS
International Policy Analyst, Europe Office
Office of Global Policy and Strategy

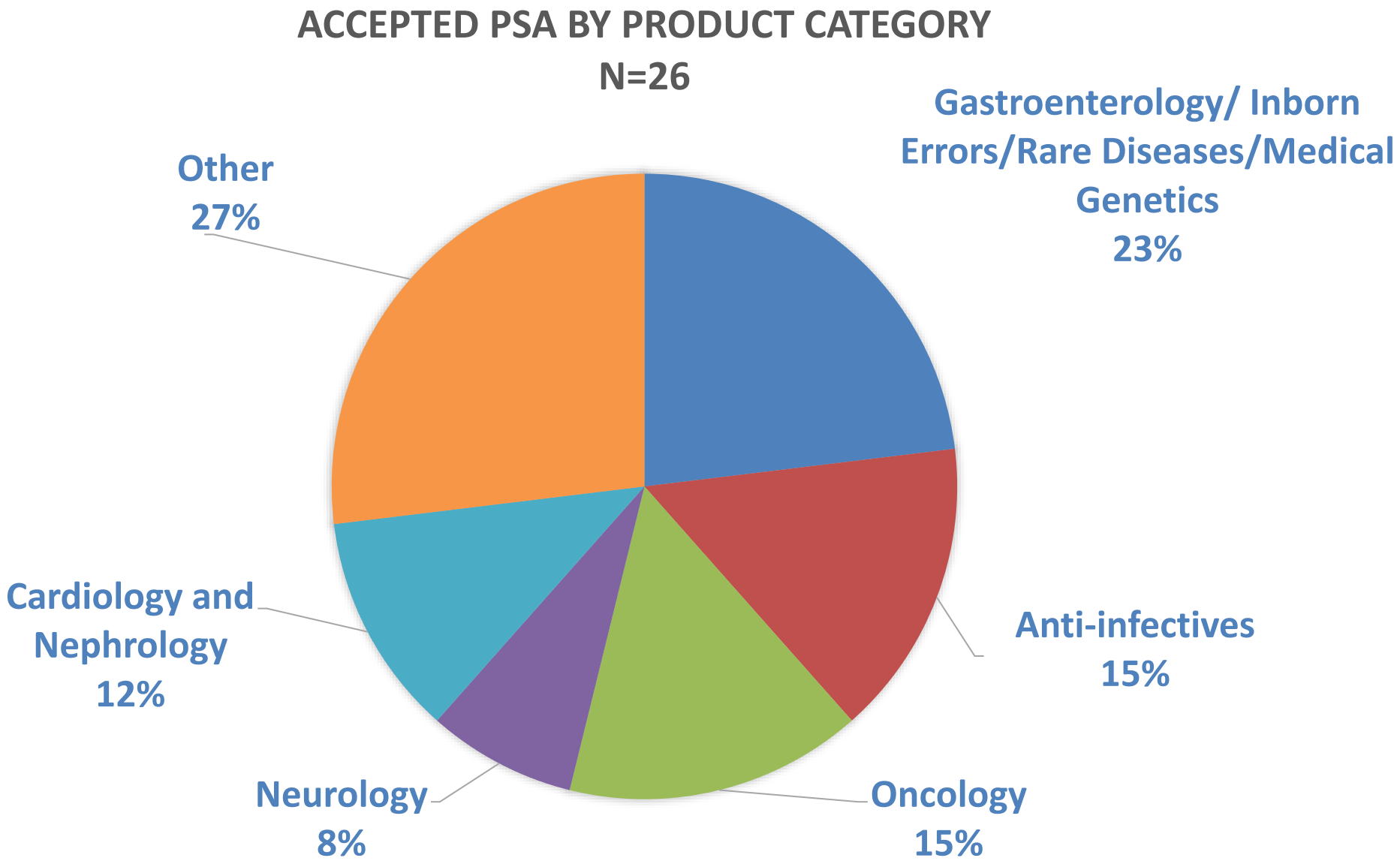
PSA Five Year Review: 2017-2021

Total Requests	37
Accepted Requests	26 (70%)
Withdrawn/Package not Submitted	4 (15%)
Completed Procedures	22

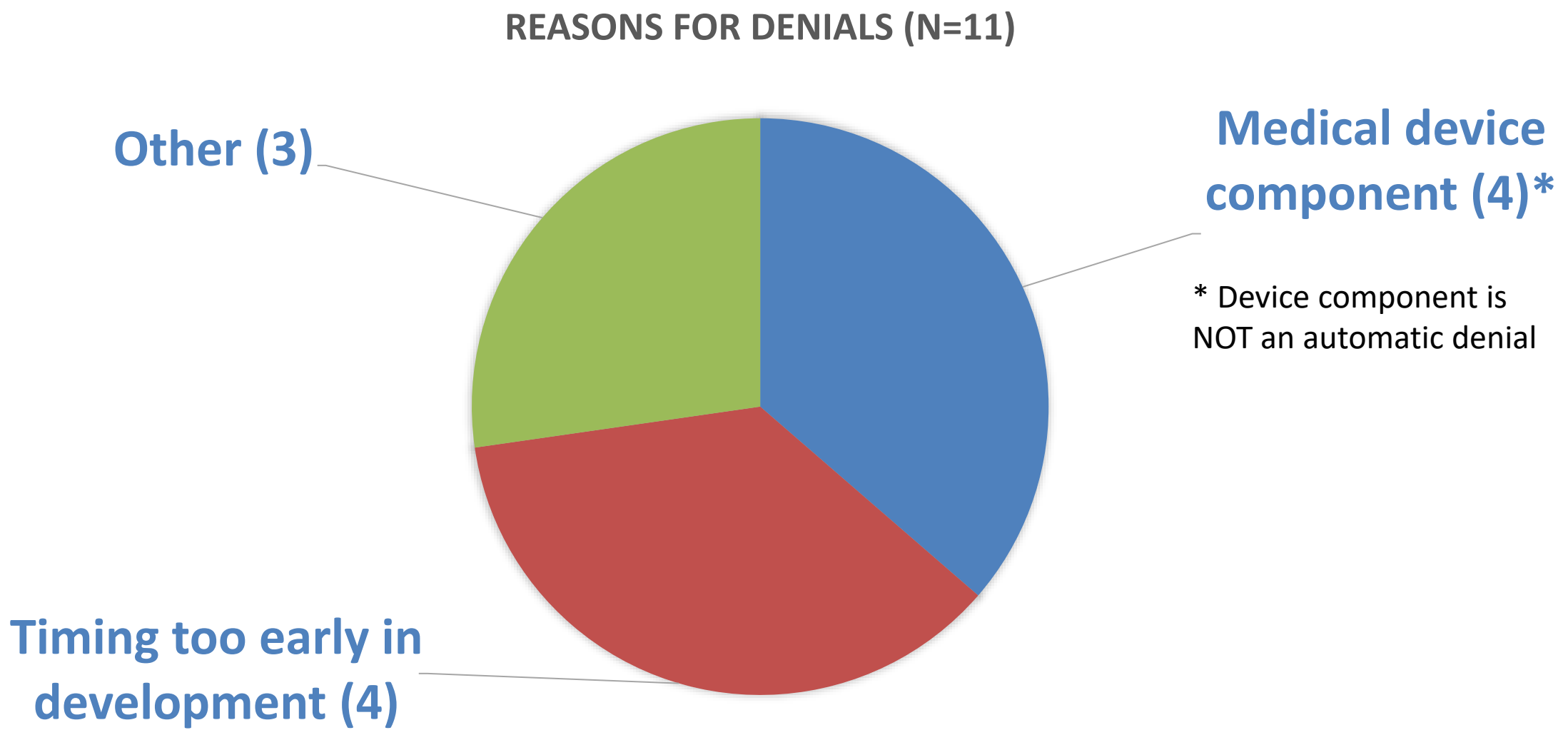
PSA Five Year Review: 2017-2021



PSA Five Year Review: 2017-2021



PSA Five Year Review: 2017-2021

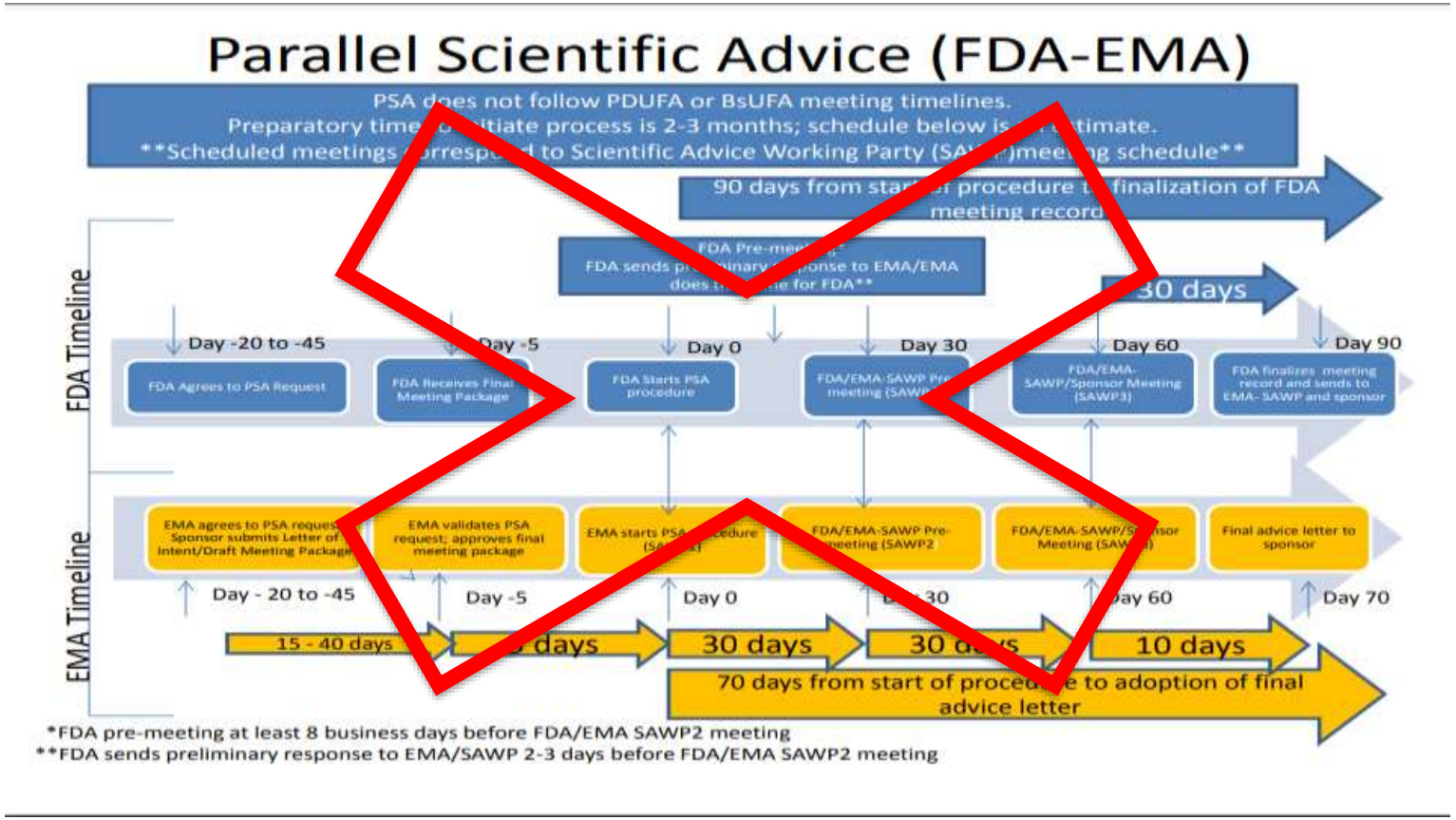


Myth-busting the Timeline

Myth #1: PSA takes too long!

Myth #2: PSA timelines are unpredictable

Myth-busting the Timeline



Examined Cohort of 2020 PSA Procedures using EMA data

- How long to accept informal request?
- How long from request acceptance to validation?
- How long from validation to Final Advice Letter?

Myth #1: PSA Takes Too Long

MYTH-BUSTED!

Average time to acceptance: **13 calendar days**

- By contrast, CDER's Type B meeting requests are allowed 21 days for review

Average time from meeting package validation to advice letter (EMA): **79 days**

- Published PSA Timeline reference is 75 days

Myth #2:PSA Timeline Unpredictable

MYTH-BUSTED!

- 2020 cohort data shows that the published PSA timeline is **highly predictable** once the meeting package is validated
- Greatest variability is in the validation phase when the ***Applicant*** has increased control of the timeline
  - Average **67 days** from acceptance to validation
  - May request a pre-submission meeting with EMA
  - May have to address deficiencies in package
  - May have strategic reasons for delaying submission

PSA Timeline*

Day	FDA	EMA
Anytime	Sponsor submits informal request for Parallel Scientific Advice to FDA and EMA; Agencies decline → no PSA Agencies accept → Sponsor begins drafting meeting package according to SAWP procedures	
Day -1 to -45		Meeting Package Submission and Validation Phase; Option for preparatory meeting with EMA according to SAWP procedures
Day 0	FDA receives validated meeting package	EMA validates meeting package
Day 5		EMA procedure begins (SAWP1)
Day 15-25	FDA internal meeting	EMA SAWP internal discussion
Day 30-34	FDA sends Preliminary Comments to EMA	EMA sends List of Issues to FDA
Day 35	Bilateral FDA/EMA meeting (SAWP2)	Bilateral FDA/EMA meeting (SAWP2)
Day 65	Trilateral Sponsor/FDA/EMA meeting (SAWP3)	Trilateral Sponsor/FDA/EMA meeting (SAWP3)
Day 75 to 95	FDA issues final meeting minutes (30 days after trilateral)	EMA issues final advice letter (10 days after trilateral)

*PSA does not follow PDUFA or BSuFA meeting timelines. Preparatory time to initiate process is 2-3 months; schedule above is an estimate. Scheduled meetings correspond to Scientific Advice Working Party (SAWP) meeting schedule.

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FDA/EMA Parallel Scientific Advice (PSA) - Two case studies

FDA/EMA Parallel Scientific Advice - Webinar

Presented by Thorsten Vetter, MD
Senior Scientific Officer, Scientific Advice Office, European Medicines Agency (EMA)

Agenda

Two anonymised recent PSA cases:

- PSA request letter – elements which supported PSA acceptance
- Topics raised for discussion
- Procedural flow/experience
- Sponsor feedback for Case 1
- Involvement of EMA Committees/Working Parties/Patients for Case 2

Background and PSA request letter

- Small molecule immunomodulator - treatment of IBD

  ⇨ change of previously agreed paediatric development

- Request letter described the challenge:
  - rare sub-population
  - inability to recruit sufficient adolescent patients in a Phase 3 study
- Development discussed previously with both FDA and EMA
  - agreed EMA Paediatric Investigation Plan (PIP)
  - Agreed FDA Initial Paediatric Study Plan (iPSP)

Background and PSA request letter

Expected PSA benefits:

- Facilitate globally harmonised approach to evidence generation in the paediatric population
- Facilitate amendments to agreed PIP (EMA) and iPSP (FDA)
- New extrapolation based proposal had been informally and independently discussed with FDA and EMA experts and views were divergent

Clear objective for PSA:

- Trilateral discussion on paediatric development programme acceptable to FDA and EMA in an area of unmet medical need

Questions raised

- Focus on the design of a new Phase 2/3 safety, efficacy, PK and PD study in the paediatric population:
  - study population
  - age cohorts
  - endpoints
  - sample size
  - statistical analysis plan
  - safety monitoring
- 'FDA-only' question on the amendment of the iPSP
- 'EMA-only' question on the overall paediatric evidence generation plan to support benefit/risk assessment in the EU

Procedural flow – acceptance to start of procedure

- PSA acceptance 10 days after request letter submission
- The sponsor immediately communicated envisaged procedural timelines
- FDA and EMA procedural leads convened a call and agreed on procedural timelines
- 6 weeks after acceptance, the draft package received for EMA validation review, no preparatory meeting requested
- 10 weeks after acceptance the package was validated

Procedural flow – start to trilateral meeting

- The published PSA timelines were met
- FDA/EMA bilateral meeting 5 weeks after procedure start
- EMA List of Issues provided 2 weeks before the trilateral meeting
- FDA preliminary answers provided 1 week before the trilateral meeting
- Sponsor considered the preliminary feedback from both Agencies and integrated into a trilateral meeting presentation as well as providing written answers

Procedural flow – trilateral meeting to written advice

- Trilateral meeting 8 weeks after start of the procedure
- Sponsor drives trilateral meeting - integrating and prioritising issues raised by both Agencies to make best use of the 90 min meeting
- After the trilateral meeting, FDA and EMA have a 30 min debriefing discussion
- Sponsor provided minutes 4 days after the meeting
- EMA Final Advice Letter shared 10 weeks after procedure start
- Time from PSA request to Final Letter: 20 weeks
- Final advice letters are exchanged between Agencies for information

PSA **benefits** based on Sponsor feedback

- Preparation of single meeting package saved time and resource
- Significantly faster alignment on a complex paediatric study design for a multinational paediatric clinical trial: 5-6 months from request to receipt of final advice
- Similar to time needed for consulting with one Agency
- PSA process facilitated detailed understanding of FDA and EMA positions
- Final study design proposal met expectations of both Agencies

PSA **challenges** based on Sponsor feedback

- Trilateral meeting:
  - Careful preparation is key
  - challenging to discuss all topics, prioritisation needed
  - advisable to provide written answers to all issues prior to the meeting
  - Separate preliminary feedback from FDA and EMA at different time points
  - Limited time (approx. 1 week) to prepare slide presentation
- Preference to receive FDA/EMA consolidated feedback or separate feedback but at a similar time point
- Detailed work on trilateral meeting presentation and written answers is key

Sponsor perception

- PSA very helpful to get alignment from FDA and EMA expeditiously when a significant change to the previously agreed clinical paediatric strategy was proposed
- Allows for detailed understanding of FDA and EMA thinking

FDA and EMA perception

- PSA worked well to agree on strategy in a rare paediatric population
- Provided a good basis for further separate discussion on detailed protocol
- Challenges mentioned by the Sponsor are acknowledged
- Receiving separate preliminary feedback may however facilitate a clear understanding of each Agency’s position when preparing the trilateral meeting

Background and PSA request letter

- Gene therapy medicinal product (ATMP)
  - Haematopoietic stem and progenitor cells (HSPC) transduced ex-vivo by a gene carrying lentiviral vector for treatment of an enzyme deficiency syndrome
- Orphan designation in US and EU
- Scope: all areas of development (CMC/NC/Clin)
- Ultra-rare population
- Focus on CMC requirements and design of a single pivotal clinical study
- ensure regulatory alignment before initiation of the single pivotal trial
- Earlier development had been discussed previously with FDA and EMA
- Sponsor informally explored PSA options with both Agencies

PSA request letter

- Sponsor suggested handling of CMC questions in writing given the high number of questions
- Clear indication of Questions addressed to both FDA and EMA and few Questions to either Agency addressing region specific considerations
- envisaged procedural timelines indicated facilitating efficient procedural planning

Questions raised - CMC

- Drug substance manufacturing
- Comparability assessment for new manufacturing process
- Batch analysis and stability data for lentiviral vector use
- Product release specifications
- Potency assay

Questions raised – Non-Clinical and Clinical

- Overall non-clinical strategy
- Design of a single pivotal Phase 3 study:
  - general design principles: single arm design, use of historic controls
  - study population
  - primary and secondary efficacy endpoints
  - composition of historical comparator cohort
  - statistical analysis plan

Questions to EMA

- Suitability of envisaged evidence generation to demonstrate ‘Significant Benefit’ in the context of the EU Orphan Designation
- Paediatric development plan

Question to FDA

- Considerations on eligibility for Rare Pediatric Disease Product Application

EMA working parties/committees/patients

- Scientific Advice Working Party (SAWP) as procedure lead
- Committee for Advanced Therapy Medicinal Products (CAT)
- Paediatric Committee (PDCO)
- Committee for Orphan Medicinal Products (COMP)
- Biologics Working Party (BWP) for CMC aspects
- Committee for Medicinal Products for Human Use (CHMP) adopted the final letter
- Two patient representatives

First PSA to discuss ATMP related CMC aspects

- CMC topics acceptability explored informally before request
- Option considered during a ATMP cluster meeting and welcomed
- During PSA, CMC aspects were discussed in separate bilateral meeting
- Main bilateral meeting focused on non-clinical and clinical issues
- There was good agreement on CMC aspects between Agencies' experts
- CMC Questions could be included for discussion at the trilateral meeting, but this was not required here
- FDA and EMA CMC experts considered discussions helpful and welcome future opportunities to discuss CMC aspects of complex products/ATMPs as part of formal PSA

Conclusion

- PSA is a useful and efficient way to align complex global development programmes
  - Innovative products
  - Areas with lacking/diverging regulatory guidance
  - Products targeting challenging populations
- Informal conversations with FDA and EMA contact points/International Offices can be helpful to prepare a PSA request
- PSA General Principles provide necessary information for efficient planning
- Timelines are met
- Increasing number of PSA procedures suggest an increasing appreciation by Sponsors as well as EMA and FDA experts

Considering a PSA Request?

Summary and Best Practices

Sandra L. Kweder, MD
Deputy Director, Europe Office
Office of Global Policy and Strategies
US Food and Drug Administration

Challenge Question 1

When EMA and FDA consider whether to grant a PSA request, they consider which of the following factors?

A. Public health benefit of the product
B. Likely cost of the product being developed
C. Potential to address unmet medical need
D. How easy the product is to manufacture
E. A and C
F. All of the above

Challenge Question 2

What percentage of all PSA requests from 2016-2020 were accepted by both Agencies?

A. 25%
B. 42%
C. 58%
D. 70%

Parallel Scientific Advice

PSA 101

It Is

- Scientific advice on product development to support a global program
- Mechanism that brings two regulators to the table simultaneously
- Opportunity to learn how aligned they are

It Is Not

- Guarantee of FDA and EMA alignment
- A substitute for sound scientific planning
- The end of the story

General Principles for PSA document
https://www.fda.gov/media/105211/download

Myths abound

- Timelines are within expected for similar processes
- Most variability in timelines depends on applicants and how long it takes between initial inquiry and a sound briefing book
- Once the process is underway you will be able to predict when you will have your advice

Experience tells the story

- PSA is a “work up front” process
- Prepared sponsors have the best experience
  - Data backs up proposals
  - Seek to foster discussion
  - Prepared to expand thinking
- Prepared agencies have good experiences
  - Informed, thoughtful experts
  - Work through internal differences ahead of meeting
- Rewarding experience for sponsors, EMA and FDA

Best Practices 1

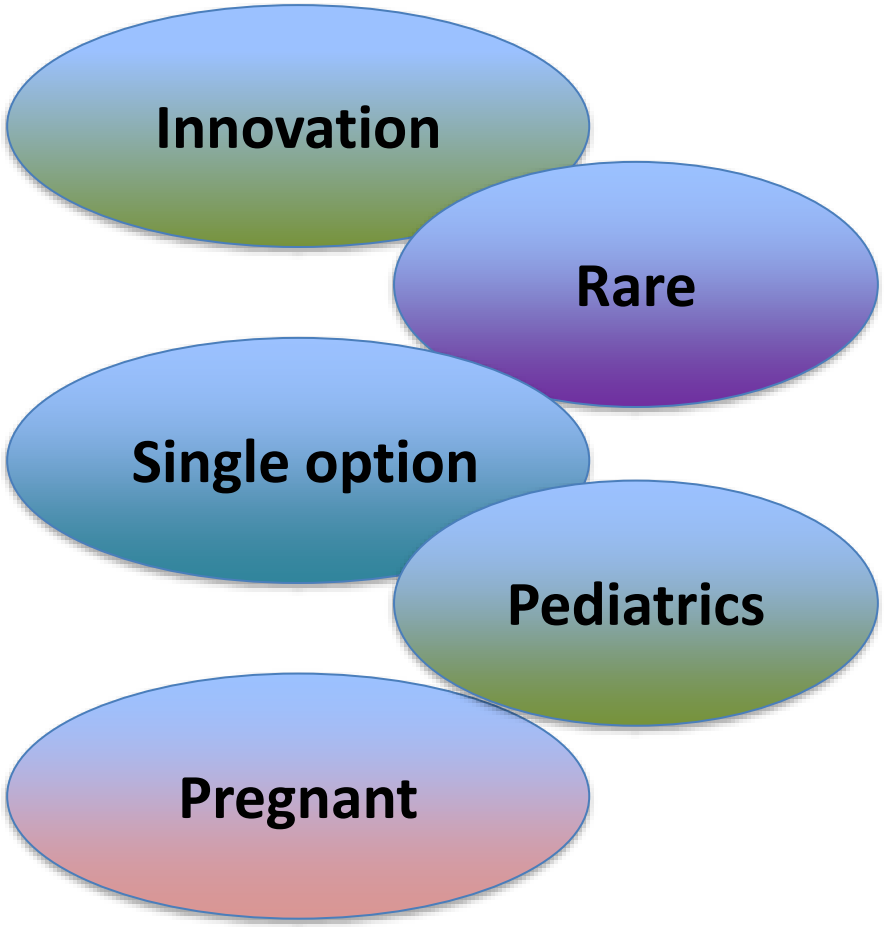
Timing matters

- PSA should not be your first discussion with FDA on development
  - Prior pre-IND or IND
  - Allows PSA to focus on global development
- Factor in calendar
  - Agencies' timelines reliable
  - Expect 2 weeks to reply to informal request
  - August recess of SAWP

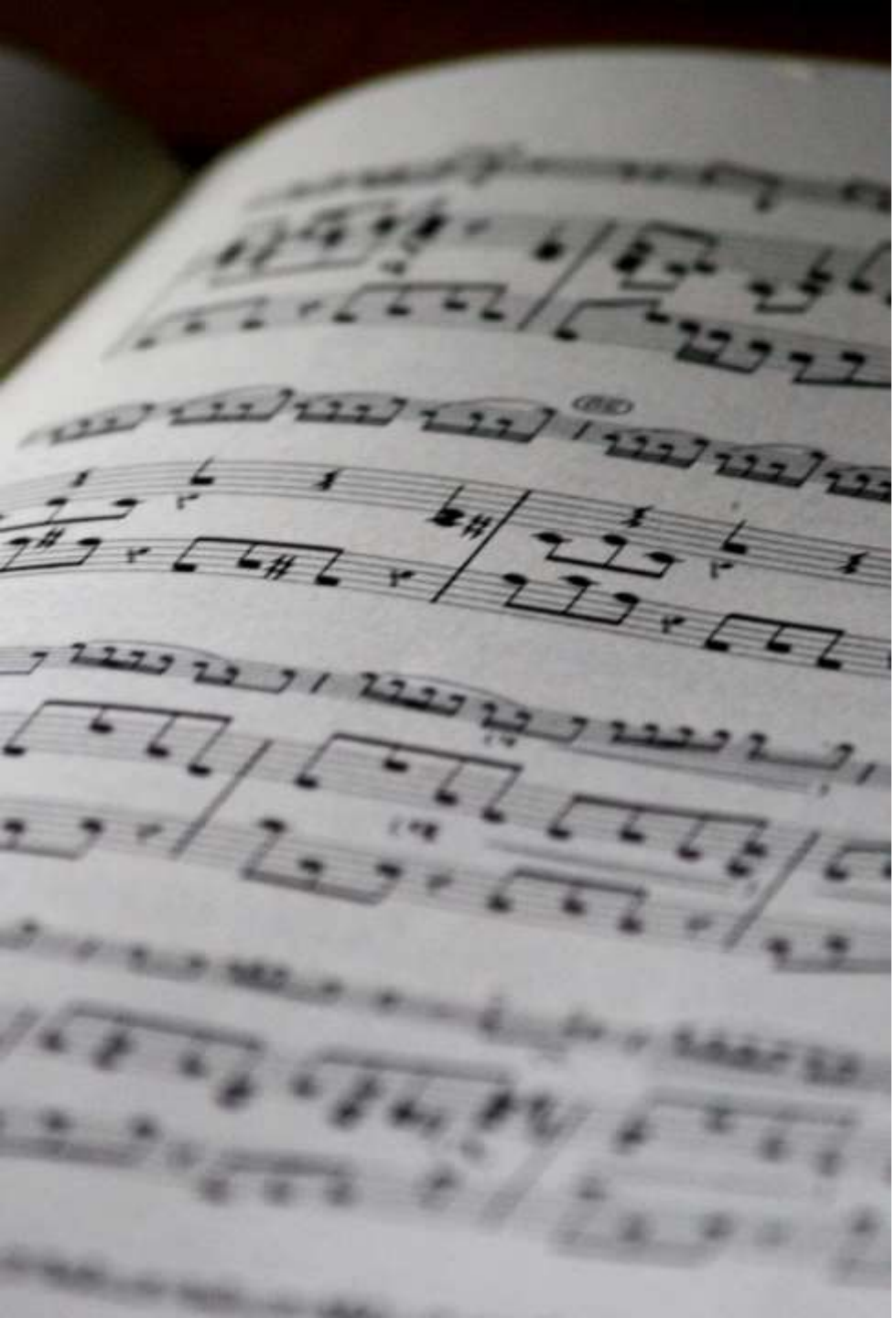
Best Practices 2
Best candidates

- Check FDA and EMA guidelines
  - If agencies already aligned PSA may not have added value
- Best candidates
  - Innovative products
  - New science
  - Novel regulatory concepts

Best Practices 3
Make the case for public health value



- Unmet medical need
- Rare diseases
- Special populations
- Explain product potential
- Be specific!



Best Practices 4
Briefing materials

- Single book for both agencies essential
  - CHMP Scientific Advice template
- Be clear on priorities
- Think through issues and options – then be candid about plans
- Label questions for one agency or both

Best Practices 5:
The Trilateral Meeting

- Prepare well
- Use preliminary feedback
- Prioritize
- Foster discussion
- Prepare your whole team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