NBOp Industry Experiences

Author: Bjørg Hunter (Novo Nordisk A/S), EFPIA
Date: 27/Nov/2020 Version: 4 (final)






The road to clarity

The road to clarity

July 2018 - Position paper on Art 117

- Advocate for parallel review

August 2018 – Industry letter to EMA (DG SANTE & DG GROW)

- Create awareness of the challenges for industry in relation to Art 117

EBE-EFPIA Reflection Paper: An Industry Perspective on Article 117 of the EU Medical Devices Regulation and the Impact on how Medicines are Assessed

By mail and e-mail

Mr Salvatore D'Acunto
Head of Unit, D4- Health Technology and Cosmetics
Directorate General for Internal Market, Industry, Entrepreneurship and SMEs (DG GROW)
European Commission
Building BREY
1049 Brussels
Belgium

Dr Andrzej Rys
Director, B – Health systems, medical products and innovation
Directorate General Health and Food Security (DG SANTE)
European Commission
Building B232
1049 Brussels
Belgium

Brussels, 26 July 2018

Dear Mr D'Acunto and dear Dr Rys,

Subject: Article 117 of Regulation (EU) 2017/745 of the European Parliament and the Council on medical devices, as it amends Directive 2001/83/EC on the Community code relating to medicinal products for human use

The road to clarity

July 2018 - Position paper on Art 117

- Advocate for parallel review

August 2018 – Industry letter to EMA (DG SANTE & DG GROW)

- Create awareness of the challenges for industry in relation to Art 117

June 2019 - End to End Control Strategy for DDCs

- End-to-end Risk based approach
- Aligning with ICH guidelines and Drug Product control
- Manufacturing controls do not need to fully rely on release testing

July 2019 - Clinical requirements for DDCs

- Clinical requirements for medicinal products take precedence
- Medicinal product requirements cover medical device requirements
- Risk based approach advocated

August 2019 Labelling requirements for DDCs

- Review issues in relation to GSPR point 23.
- Industry perspective is that medicinal directive takes precedence
- IFU can be in scope of NB review in relation to DDC function
- Clarification requested

December 2019 – Substantial change

- Risk based approach
- Encourage variation guideline to be updated

December 2019 – GSPR case study for a prefilled pen

- Case study of GSPR compliance for Art 117 for a prefilled pen
- Examples of which GSPRs will likely apply and which are covered by medicinal product regulation.

The road to clarity

July 2018 - Positioning paper on Art 117

Advocate for parallel review

Augus

Crea

June 2

Risk

Aligr

Man

July 2

Clini

Med

Risk

Augus

Revi

Indu

IFU c

Clari

Dece

Risk

Encourage variation guideline to be updated

December 2019 – GSPR case study for a prefilled pen

Case study of GSPR compliance for Art 117 for a prefilled pen

Examples of which GSPRs will likely apply and which are covered by medicinal regulation.

EBE-EFPIA Reflection Paper: An Industry Perspective on Article 117 of the EU Medical Devices Regulation and the Impact on how Medicines are Assessed

EMA

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

CMDh
Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human

21 October 2019 Rev.1
EMA/37991/2019
Human Medicines Evaluation Division

Questions & Answers on Implementation of the Medical Devices and In Vitro Diagnostic Medical Devices Regulations ((EU) 2017/745 and (EU) 2017/746)

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

1 29 May 2019
2 EMA/CHMP/QWP/BWP/259165/2019
3 Committee for Medicinal Products for Human Use (CHMP)
4

5 Guideline on the quality requirements for drug-device
6 combinations
7 Draft

TEAM NB

TEAM NB
The European Association Medical Devices - Notified Bodies

Editor : Team-NB	Adoption date : 01/04/2020	Version 1

Team-NB Position Paper

on Documentation Requirements for Drug Device Combination Products

Falling in the Scope of Article 117 of MDR 2017/745.

Topic 1: Requirements on the submission file´s documentation (structure)

Each Notified Body is a separate, non-governmental organization and thus offers its own specific organizational setup. This organizational setup includes specific processes and specific interfaces on client interaction.

In consideration of this organizational setup of Notified Bodies, the requirements on the submission file format should only focus on general documentation related requirements, i.e. the structure and contents as well as the format related to the documentation submitted. The way of documentation submission to the respective Notified Body, the way of documentation handling, storage and archiving at the respective Notified Body are out of scope.

According to the second subparagraph of Article 117 (Regulation (EU) 2017/745 on medical devices (MDR)), the opinion issued by a notified body applies to "the conformity of the device part with the **relevant general safety and performance requirements set out in Annex I (GSPRs)** to that Regulation" ("that Regulation" being the MDR).

For medical devices being solely governed by the MDR, the documentation requirements related to the GSPRs are described in Annex II Technical Documentation (MDR, Annex II; in specific section 4). These documentation requirements should also be considered for the documentation of the device part.

Version N° 1 of 11 December 2019

Final

Executive summary

Article 117 of the Medical Device Regulation (EU) 2017/745 (MDR) requires the Marketing Authorization Applicant to include a Notified Body Opinion on the device constituent, part of a single integral Drug-Device Combination (DDC) in the Marketing Authorization Application, from 26 May 2020. With that, the applicant must demonstrate conformity with the relevant General Safety and Performance Requirements (GSPRs) as outlined in MDR's Annex I.

The road to clarity

July 2018 - Positioning paper on Art 117

Advocate for parallel review

Augus

Crea

June 2

Risk

Aligr

Man

July 2

Clini

Med

Risk

Augus

Revi

Indu

IFU c

Clari

Dece

Risk

Encourage variation guideline to be updated

December 2019 – GSPR case study for a prefilled pen

Case study of GSPR compliance for Art 117 for a prefilled pen

Examples of which GSPRs will likely apply and which are covered by medicinal regulation.

EBE-EFPIA Reflection Paper: An Industry Perspective on Article 117 of the EU Medical Devices Regulation and the Impact on how Medicines are Assessed

EMA

EUROPEAN MEDICINES AGENCY
SCIENCE

CMDh

21 October 2019 Re
EMA/37991/2019
Human Medicines E

Questions
Devices ar
Regulation

1 29 May 2019
2 EMA/CHMP/QWP/B
3 Committee for Med
4

5 Guideline
6 combinations
7 Draft

TEAM NB

Ongoing guidance development within MDCG Subgroups – October 2020*

*This is not an exhaustive list of ongoing work performed by MDCG subgroups

Scope	Group Deliverables	Consult prior to MDCG**	Planned MDCG Endorsement	Additional Comments
** Stakeholders are observers in 13 MDCG subgroups and are consulted on a regular basis; further to that other MDCG subgroups are consulted as indicated				
1. Notified Bodies Oversight (NBO)[1]				
MDR + IVDR	*Q&A on requirements notified bodies –new questions to be added to MDCG 2019-6*	Notified bodies	2020	
MDR + IVDR	*Q&A related to MDCG 2020-4*		2020	
MDR+IVDR	*Updates of guidance documents and templates on the designation and re-assessment process*	Notified bodies	2021	
MDR + IVDR	*Updates of guidance documents and templates on qualification and authorisation of personnel*	Notified bodies	2021	
MDR + IVDR	*Guidance on Certifications according to Article 16 MDR/IVDR)*		2021	Jointly with the Market Surveillance WG
MDR	*Guidance on appropriate surveillance according to Article 120(3)*		2021	
MDR	*Guidance on NB opinions on the conformity of the device part according to Article 117 MDR*	B&C		
IVDR	*Endorsement on codes*	IVD, notified	Q1 2021	

/2020 Version 1

ion Products

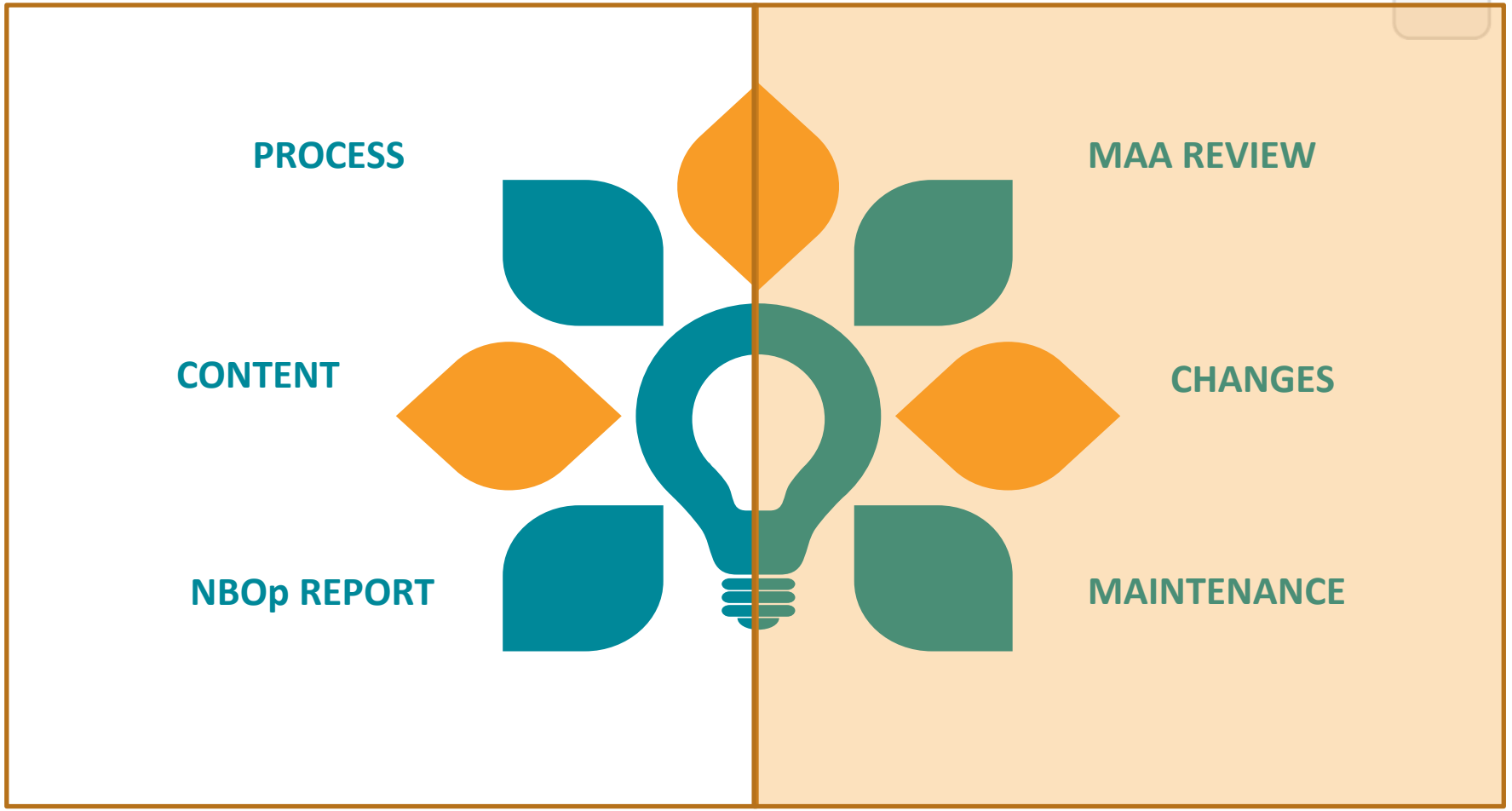
ation (structure)

Executive summary

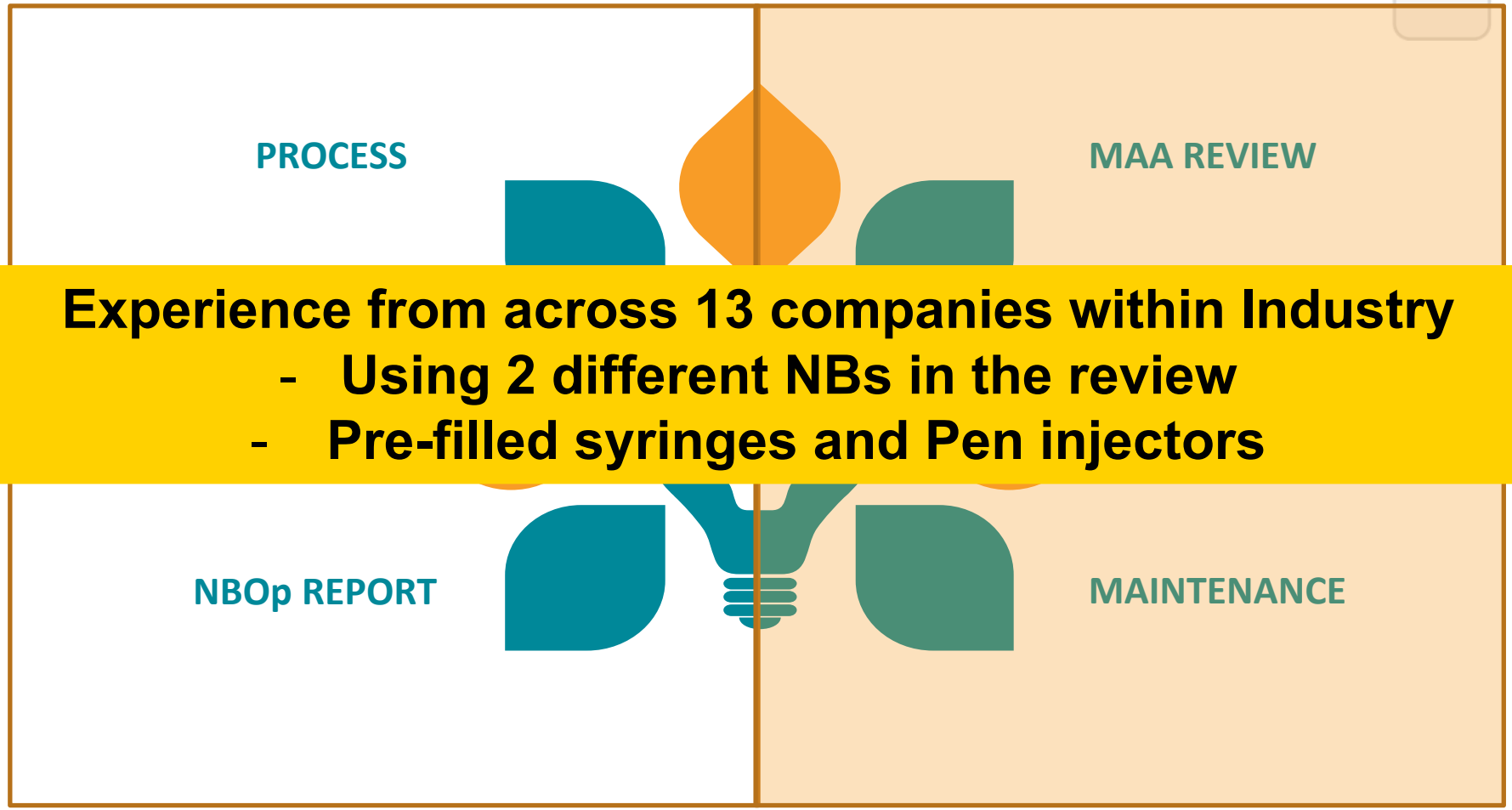
Article 117 of the Medical Device Regulation (EU) 2017/745 (MDR) requires the Marketing Authorization Applicant to include a Notified Body Opinion on the device constituent, part of a single integral Drug-Device Combination (DDC) in the Marketing Authorization Application, from 26 May 2020. With that, the applicant must demonstrate conformity with the relevant General Safety and Performance Requirements (GSPRs) as outlined in MDR's Annex I.

Remaining uncertainty

Remaining uncertainty



Remaining uncertainty



Experience from across 13 companies within Industry

- **Using 2 different NBs in the review**
- **Pre-filled syringes and Pen injectors**

Process

Process overview

Good collaboration with few points for improvements

Worked Well	
• Clear communication	
• Flexibility in review options and timeline	
• Overall timelines have been met as agreed during planning stage	
• Accelerated review possible across NBs in instances where a review has been needed in a short time frame	
• Flexibility from EMA in allowing NBOps before May 2021 and flexibility in timelines for submission.	
• Recognition that everyone is learning how to work with the new process	

Process overview

Good collaboration with few points for improvements

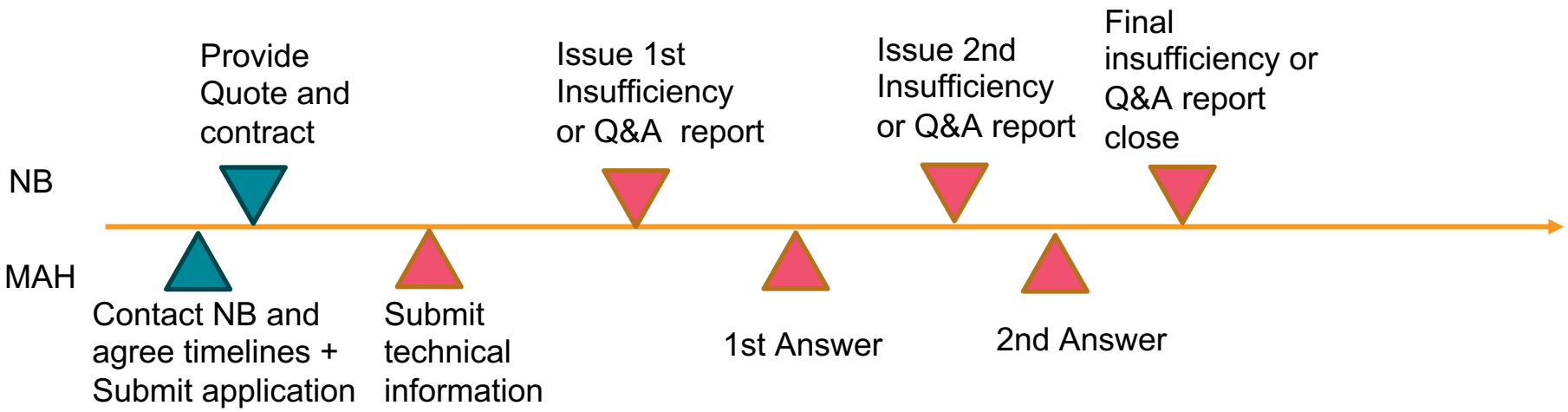
Worked Well	Points for Improvement
• Clear communication	• Access to a certified NB
• Flexibility in review options and timeline	• Availability can depend on reviewer
• Overall timelines have been met as agreed during planning stage	• Some interim timepoints not always clear (e.g. Unclear timing between finished review and report being available)
• Accelerated review possible across NBs in instances where a review has been needed in a short time frame	• Q&A rounds can be extensive and vary in length (1-5 rounds have been seen) • It is not clear what level of detail is needed
• Flexibility from EMA in allowing NBOps before May 2021 and flexibility in timelines for submission.	• Alignment with MAA possible but some data cannot be included due to timelines • What is reviewed by NB and what is reviewed by EMA – clarity needed
• Recognition that everyone is learning how to work with the new process	• How to consider established knowledge for generics and biosimilars

Process timeline

Example process overview

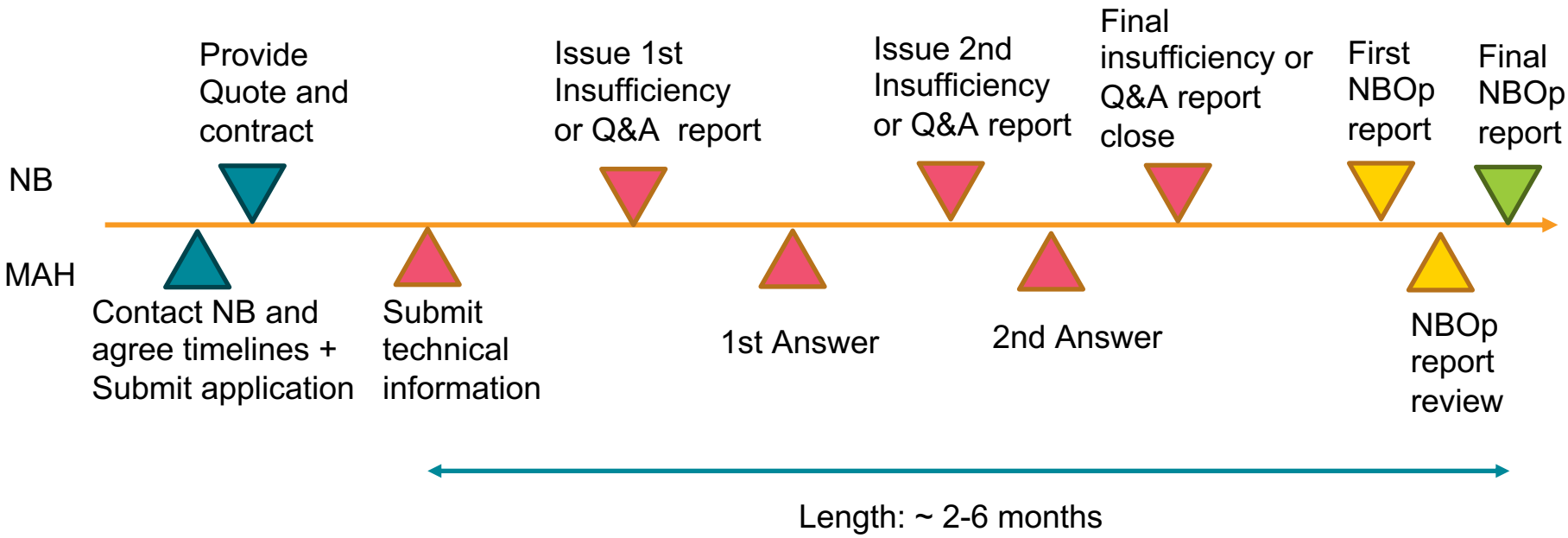
Process timeline

Example process overview



Process timeline

Example process overview



Technical Content & Review

Technical Content & Review

Different approach between NBs*

Technical Review

- Level of detail requested by NBs
- “Audit” approach v.s. “Summary review” approach
- Expectation of technical submission package

*Across 2 NBs

Technical Content & Review

Different approach between NBs*

Technical Review

- Level of detail requested by NBs
- “Audit” approach v.s. “Summary review” approach
- Expectation of technical submission package

Late-coming data

- Option of partial review offered by some NBs
- Others wanted to see full data
- Different interpretation of applicability of GSPRs

*Across 2 NBs

Technical Content & Review

Different approach between NBs*

Technical Review

- Level of detail requested by NBs
- “Audit” approach v.s. “Summary review” approach
- Expectation of technical submission package

Late-coming data

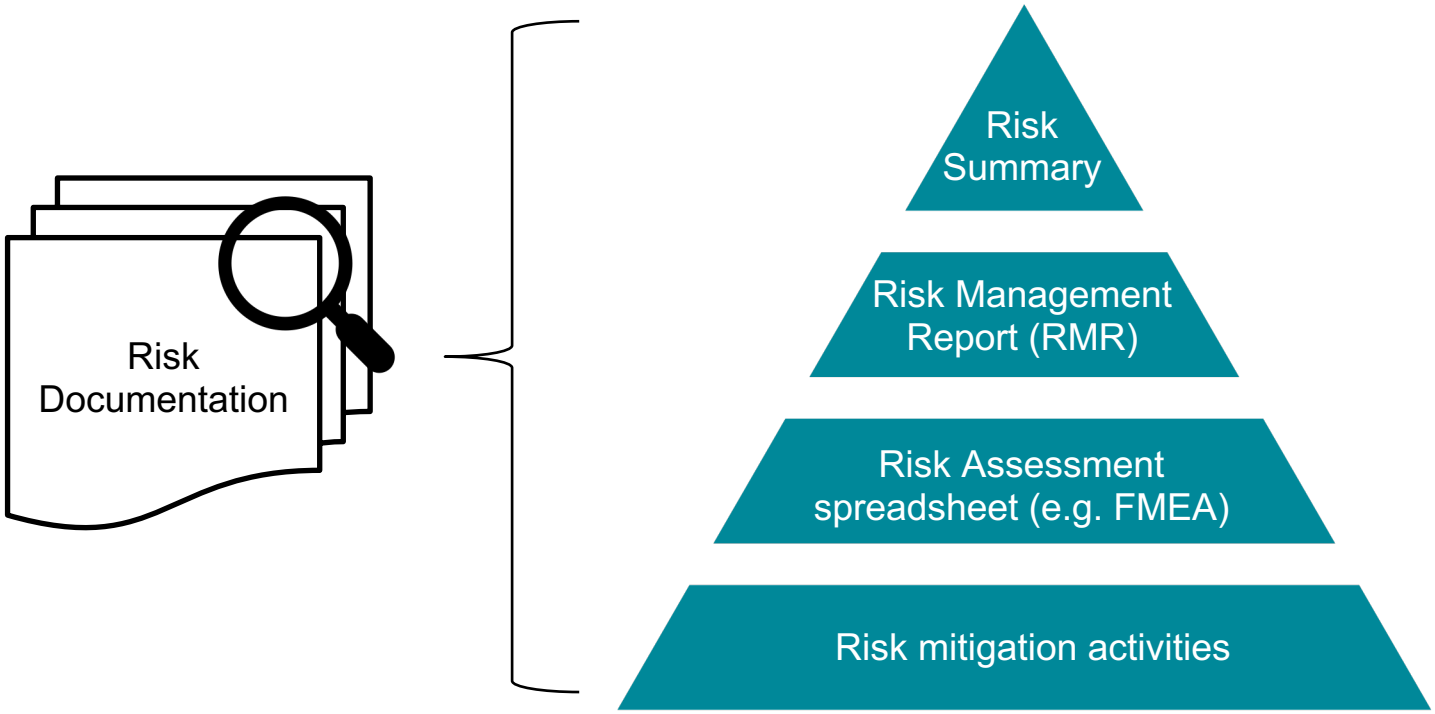
- Option of partial review offered by some NBs
- Others wanted to see full data
- Different interpretation of applicability of GSPRs

Interpretation of NBs remit vs EMAs

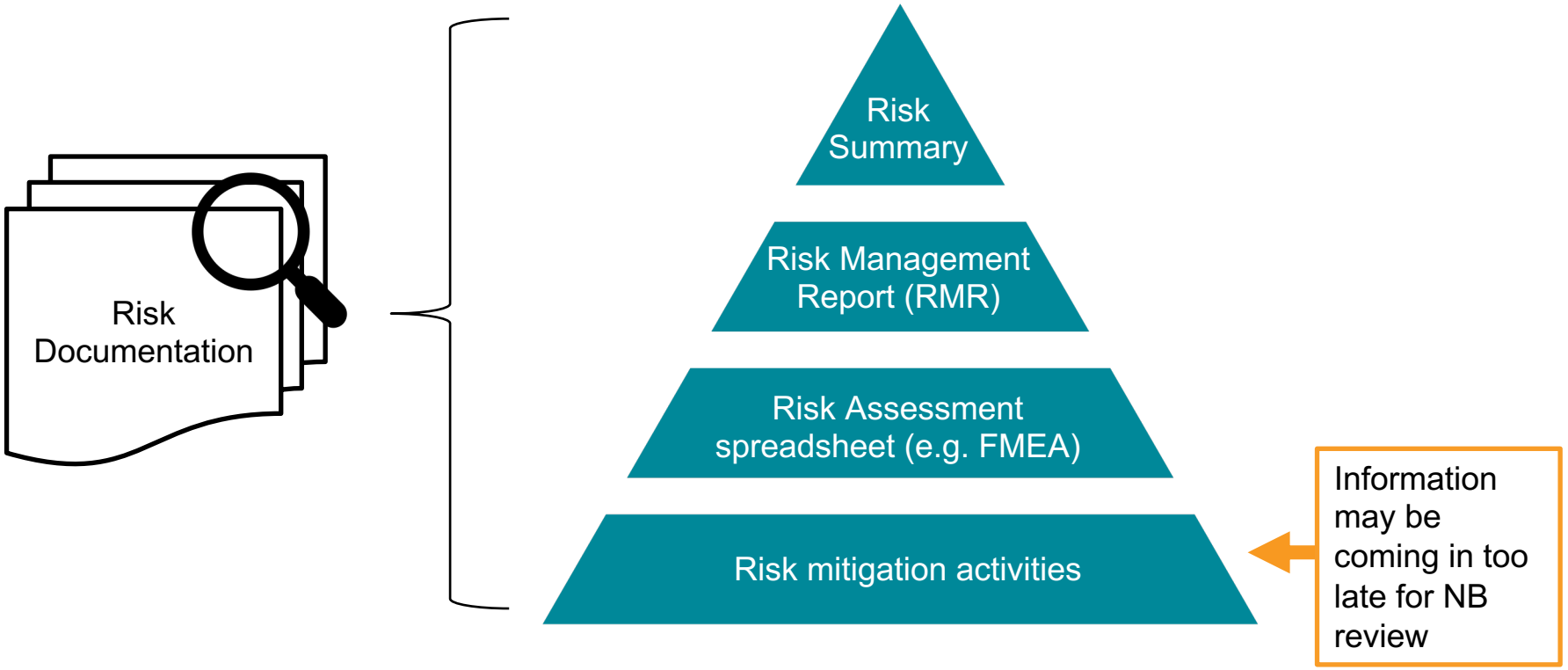
- Inconsistency in interpretation of where there is overlap with MAA especially related to late coming data
- General uncertainty of how NBOp is used by EMA

*Across 2 NBs

Technical content example



Technical content example



Notified Body Opinion

NBOp Report

NBOp content very detailed

Different Level of **detailed information in reports**

- **20 pages vs 100+ pages***

Content of report included **information copied from the technical documentation**

- **E.g. pictures, tables, detailed information**
- **Check list of GSPR applicable/reviewed or not**

NBOp has to be **reviewed by MAH** due to level of detail

- **Align level of detail with the MAA or variation and check for correctness**

* across similar devices e.g. PFS and Pre-Filled Pen

NBOp Report

NBOp content very detailed

Different Level of **detailed information in reports**

- **20 pages vs 100+ pages***

Content of report included **information copied from the technical documentation**

- **E.g. pictures, tables, detailed information**
- **Check list of GSPR applicable/reviewed or not**

NBOp has to be **reviewed by MAH** due to level of detail

- **Align level of detail with the MAA or variation and check for correctness**

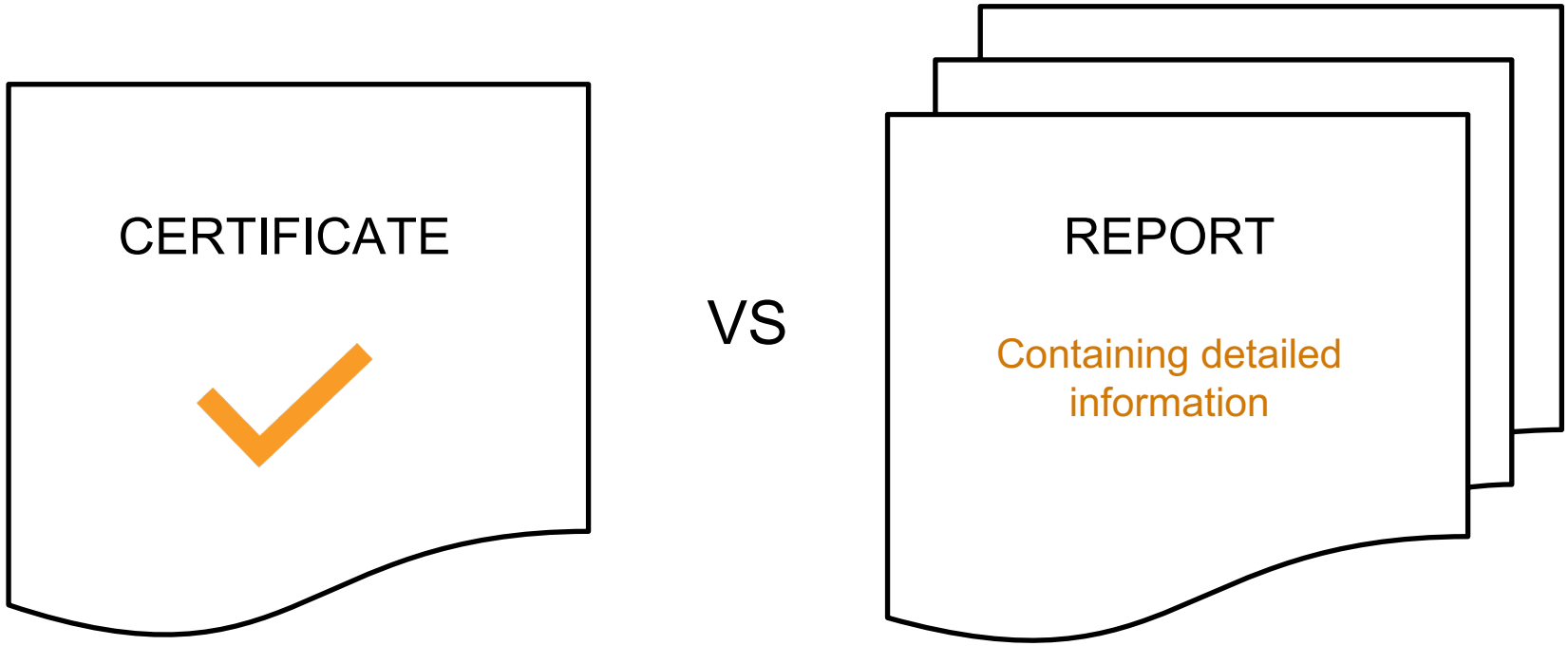
The opinion is not **"Positive"** or **"Negative"**

Report simply states what has been reviewed or "The objective of this assessment has been found to be met"

* across similar devices e.g. PFS and Pre-Filled Pen

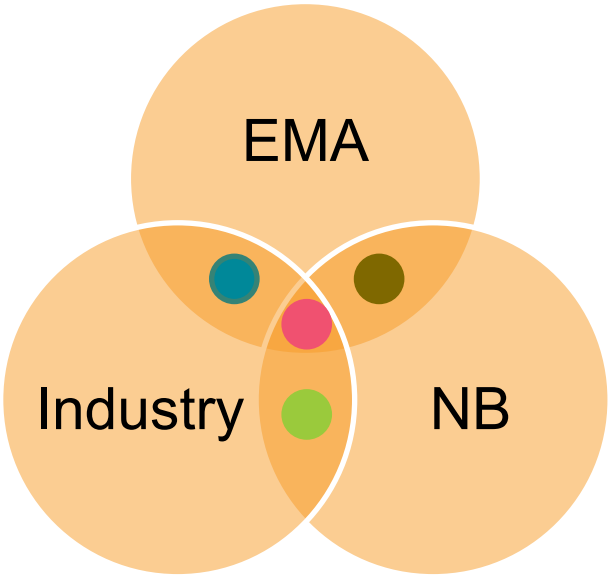
NBOp problem statement

What is the relevant level of detail for the EMA assessors?



Key Messages

Points for clarification



Clarifying Questions Across All Parties

- Is a parallel review possible?
- How will the NBOp be used during MAA review?

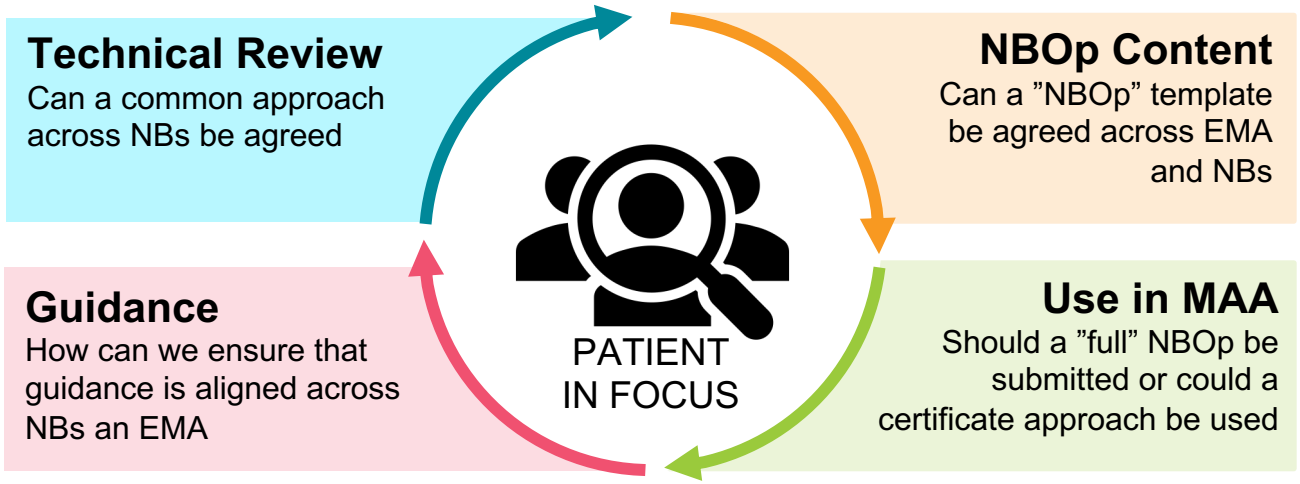
- Can clear definition of review responsibilities & specific content between NB and EMA be defined?
- How can late-coming documentation be managed?

- How can the NBOp review process and report be "standardised"?
- What is the right level of information for a review?

- What information does EMA expect to see in the NBOp?
- Can a clear general timeframe be agreed?

Key messages

There is a need to standardise across all parties



efpia
European Federation of Pharmaceutical Industries and Associations

AESGP

medicines for europe
better access. better health.

Vaccines Europe

EUCOPE
European Confederation of Pharmaceutical Entrepreneurs AISBL

MEDTECH & PHARMA PLATFORM

EUROPHARMSMC
CONNECTING & SUPPORTING PHARMA ACROSS EUROPE

Thank you