EU Paediatric Regulation

How to prepare PIP/waiwer dossier?

EMEA SME workshop

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Anu Tummavuori

Associate Director European Regulatory Liaison

Celgene, Switzerland

Overview

- EU Paediatric Regulation – what does it mean in practise?
- Where to start for PIP/waiver – what needs to be considered?
- How to get it to EMEA and pass validation?

EU Paediatric Regulation

Objectives of the Paediatric Regulation

- ✓ **Improve the health of children**
  - Increase high quality, ethical research into medicines for children
  - Increase availability of authorised medicines for children
  - Increase information on use of medicines in children
- ✓ **Achieve the above**
  - Without unnecessary studies in children
  - Without delaying authorisation for adults
- ✓ **Development of medicines for children should be an integral part of the development of medicinal product**
- ✓ **Integrated into the development program for adults**

What is a PIP?

- Roadmap to obtain paediatric indication (and formulation)
- Same criteria as for MAA (Q, S & E)
- Basis for the reward
- No “PIP light”

Need a PIP because of

Paediatric Regulation states that there is an obligation to submit results of paediatric studies compliant with PIP, or a waiver or deferral, in Module 1 of

New Products (Art 7):
- **MAA application**
- Need to cover MAA indication(s)
- All new products irrespective of patent status

Approved product (Art 8) when new indication, route of administration, formulation:
- **Variation/line-extension application***
- Need to cover all existing and new indications
- **Only products with SPC (or patent qualifying for SPC)**

*new/change to indication, new formulation, new route of administration

What does PIP & Waiver need to cover?
- Example for overview for a product

	Pre-term newborn infants	Term newborn infants (0-27 days)	Infants & toddlers (28 d - 23 m)	Children (2-11 years)	Adolescents (12-17 y)
Adult indication A	Class waiver	Class waiver	Class waiver	Class waiver	Class waiver
Adult indication B	Waiver	Waiver	PIP including deferrals & formulation development	PIP including deferrals & formulation development	PIP including deferrals & formulation development
Paediatric indication	PIP including deferrals & formulation development	PIP including deferrals & formulation development	PIP including deferrals & formulation development	Waiver	Waiver

When to submit PIP?

Products in development:

- Regulation: end of Phase 1
- Well in time for having PIP approved,
  and compliance check done before MAA filing

Products already approved:

-Well in time for having PIP approved,
and compliance check done before variation/line-extension filing

Worthwhile to consider:

- reward opportunities (timing for having Pae studies in MA)
- withdrawal/re-submission of PIP
- impact on due diligence

PIP compliance

- **Compliance =**
  verification that the measures agreed in PIP & Decision have been conducted in accordance with the decision including the timelines

- **Is needed for 2 instances**
  1) filing of MAA/extension/indication submission (unless relevant conditions waived or deferred)
  2) pre-requisite for obtaining the reward

MAA/variaon/extension validation

- **Validation =**
  verification that the applicant meets the administrative and legal dossier requirements, now including Paeditric Regulation

- **Is performed before assessment**
  if no positive validation, the assessment will not start

Validation and compliance - *Example for a product*

	Pre-term newborn infants	Term newborn infants (0-27 days)	Infants & toddlers (28 d - 23 m)	Children (2-11 years)	Adolescents (12-17 y)
Adult indication A: Subject to MAA	**Waiver**	**Waiver**	**Waiver**	**PIP***	**PIP**
Adult indication B: Subject to filing later	**Waiver**	**Waiver**	**PIP***	**PIP***	**PIP***
Paediatric indication	**PIP***	**PIP***	**PIP***	**Waiver**	**Waiver**

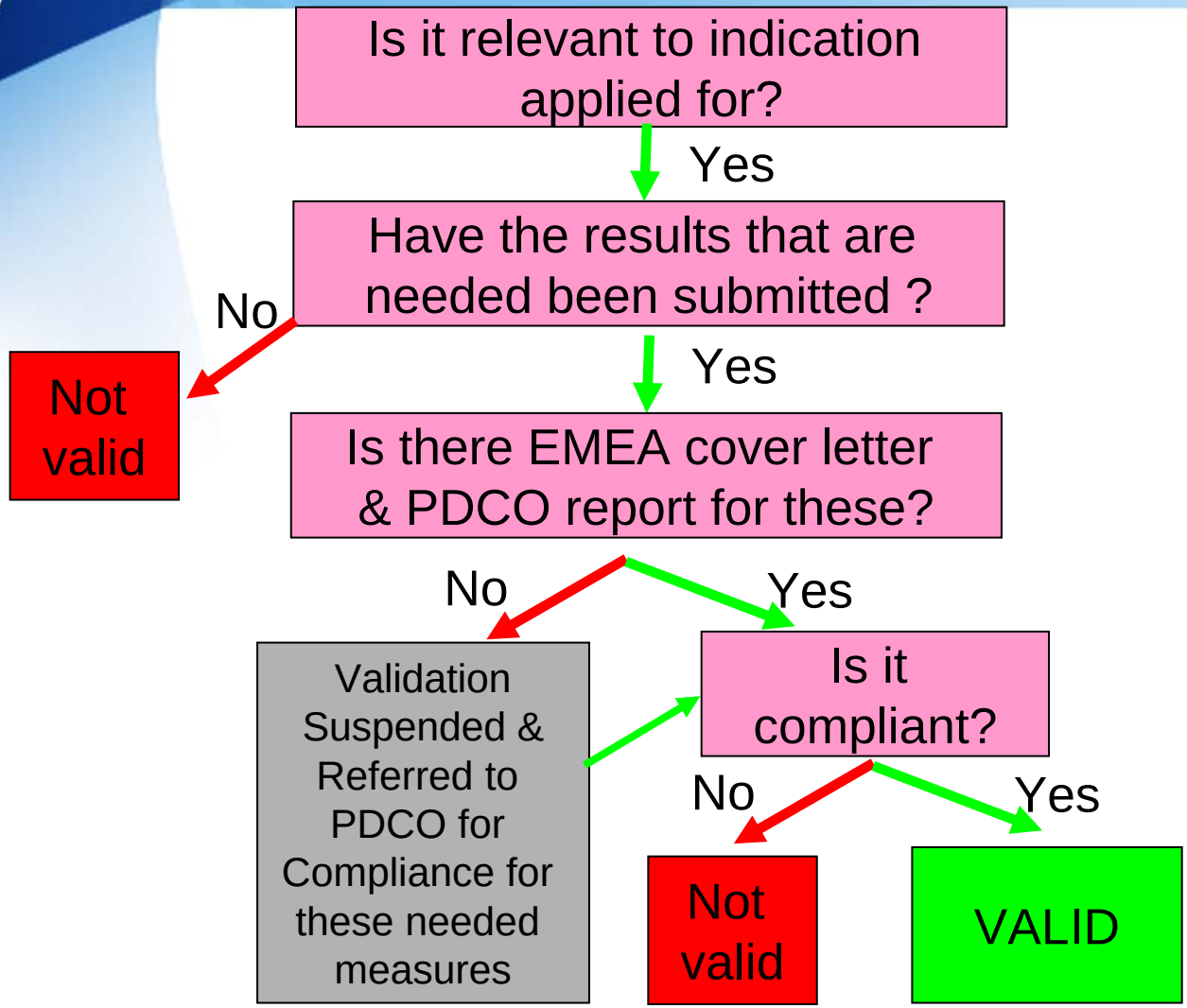
Subject to compliance for MAA validation

Subject to compliance for indication filing validation

Subject to compliance for completed PIP validation for reward

* Must include formulation development (if applicable)

Validation Decision Tree
- *PIP with (partial) deferral*



Preparing for PIP – what needs to be considered?

Question to ask about product?

- Is this a new or already approved product?
- Does the product have a SPC (patent)?
- Does the product have an Orphan Designation?
- Has/Is the product been/being registered in the US? Is there a WR?
- Are the indications/conditions applicable for paediatric population?
- Can the product be developed in other paediatric indications/conditions?

EU and US: what needs to be done?

	Chemical NME	Biotech	Orphan	Other
EU Regulation	**Mandatory for MAA and indications/ line extensions** All adult indications + pae possible **Reward possible**	**Mandatory for MAA and indications/ line extensions** All adult indications + pae possible **Reward possible**	**Mandatory for MAA and indications/ line extensions** All adult indications + pae possible **Reward possible**	**Voluntary PIP + PUMA possible for product out of patent** **Reward possible**
US PREA	**Mandatory** to include assessment, waiver or deferral in NDAs/sNDAs **No reward**	**Mandatory** to include assessment, waiver or deferral in NDAs/sNDAs **No reward**	Not applicable	Does not apply to generics, OTC
US BPCA	**Voluntary;** Written Request (WR) linked to active moiety, not NDA **Reward possible**	Not applicable	**Voluntary**; WR linked to active moiety, not NDA **Reward possible**	

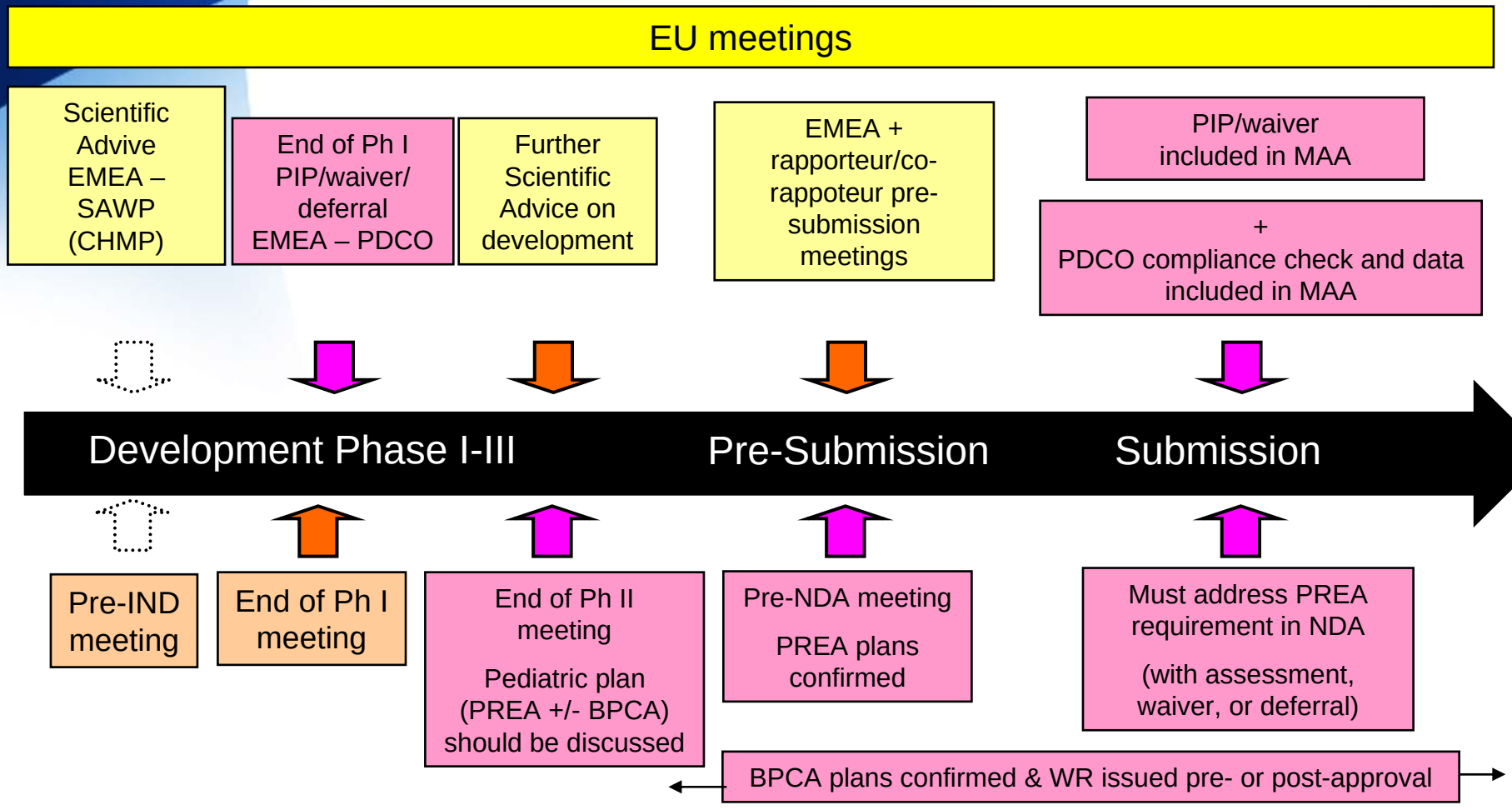
And Tummavuori

P(a)ediatric Plan + Waivers EU and US

- Possible breakdown for "novel oncology biotech product"

	Pre-term newborns	~0-1 month	~1– 24 months	~2-12 years	~12-(16) 17 years
Adult indication A: Breast Cancer	**Waiver**	**Waiver** **Waiver**	**Waiver** **Waiver**	**Waiver** **Waiver**	**Waiver** **Waiver**
Adult indication B: Leukemia	**Waiver**	**Waiver** **Waiver**	**PIP including deferrals & formulation development** **PREA plan with deferrals, formulation development**	**PIP including deferrals & formulation development** **PREA plan with deferrals, formulation development**	**PIP including deferrals** **PREA plan with deferrals**
Paediatric indication: (not planned) Medullo-blastoma	**PIP incl deferrals & formulation development**	**PIP including deferrals & formulation development** **WR not possible**	**PIP including deferrals & formulation development** **WR not possible**	**Waiver** **WR not possible**	**Waiver** **WR not possible**

Timing of pae submissions and discussions with FDA and EU regulators



The Rewards in the EU

Regulation has possibility for different rewards:

1. ***Patented products (products under patent which qualifies for SPC):***
   + 6 months SPC extension
   or
   + 1 year on MP for innovative new pae indication

2. ***Orphan Medicinal Products:***
   + 2 years extension to ME

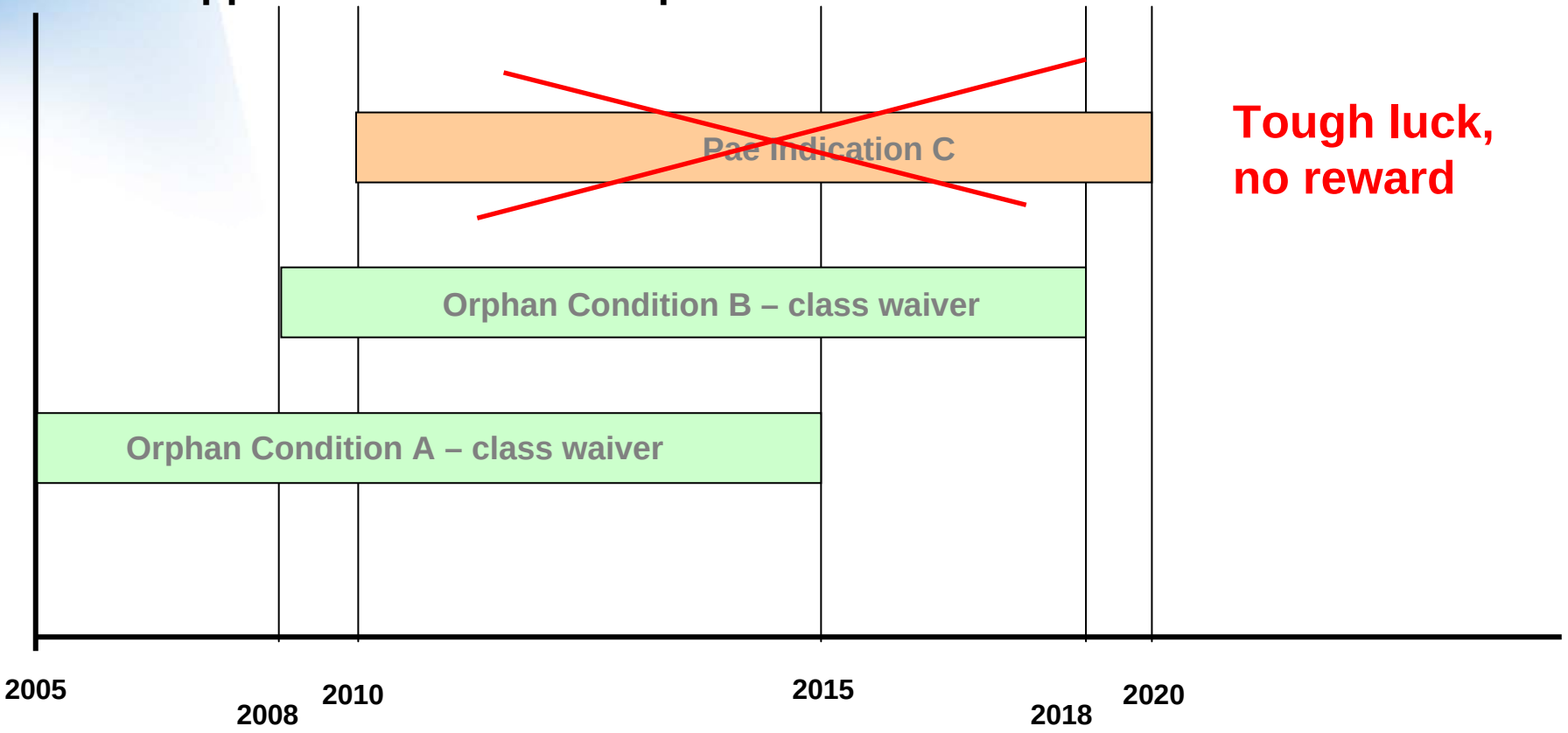
3. ***Off-patent medicinal products:***
   New type of MA: Paediatric Use Marketing Authorisation (PUMA)

Paediatric Rewards: Special inssues for OMPs

- **Reward for OMPs:**
  - 2 year extension of ME (SPC extension NOT possible)
- **Many do not have a patent**
  - Art 7 of Paediatric Regulation applies (PIP/waiver for MAAs)
  - Art 8 unclear:
    - mandatory need to have PIP/Waiver for new indications/line extensions does not apply
    - for voluntary submission clarification is being sought
- **What is the situation for OMPs with multiple ODDs?**
  - Understanding that all ODDs for which PIP has been complied and completed qualify for reward
  - no reward for waivers
  - clarification ongoing

Examples 1:

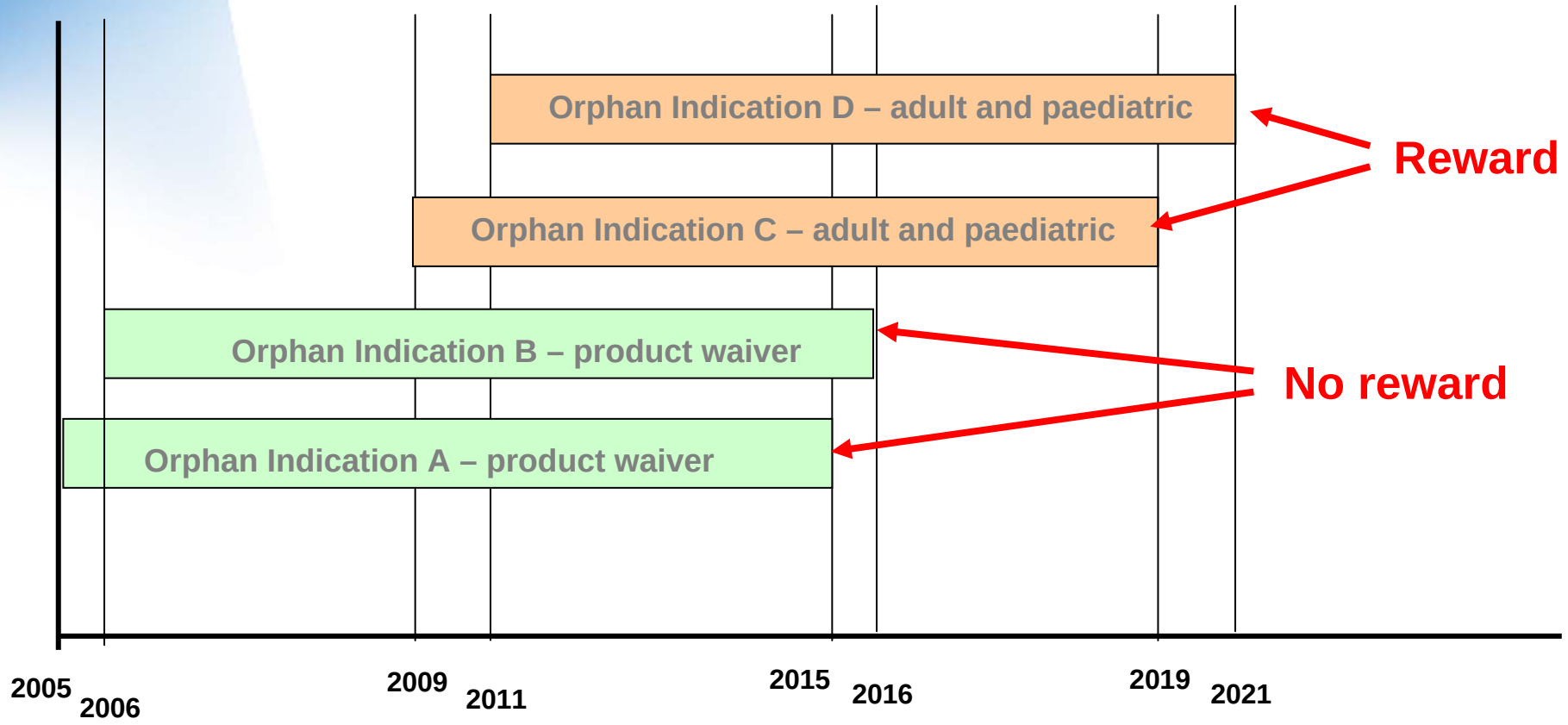
Question: what is the reward for conducting an agreed PIP in a specific orphan indication that differs from the approved orphan adult conditions, especially if the results from the paediatric studies do not result in data that supports addition of that paediatric indication in the SmPC?



Tough luck, no reward

Example 2:

Question: what is the reward?



PIP and waiver application

What info is there?

Relevant documents:

Guidance:

•European Commission guideline on format and content of applications for paediatric investigation plans
Applicants are reminded that the format of the scientific document (parts B to E) for PIP/waiver applications has changed, in accordance with the new EU guideline. The document should follow the outline published in the last page of the "Electronic template for PIP applications".
•Frequently asked questions on regulatory aspects of Regulation (EC) No 1901/2006 (Paediatric Regulation) amended by Regulation (EC) No 1902/2006 (EMEA/520085/2006). Updated 2 September 2008
•**Procedural advice** **Updated 10 June 2009**
•Contact details for PDCO members and alternates for sending PIP application

Templates:

•Template letter of intent Rev. 3 Updated 31 October 2008

•Electronic template for PIP applications or request for waiver – Updated 26 January 2009

A list of the changes in the new form is available here

To use the template you will need version 8 or above of the free Adobe Reader on your PC, which you can download here.

•Template for the PDCO Summary Report (including internal guidance - published for information
•Request for modification of an agreed paediatric investigation plan Published 28 May 2009
•Request of confirmation of the applicability of the EMEA decision on class waivers Published 21 July 2008

Deadlines* and PDCO meeting dates:

•PDCO meeting dates 2008 Rev. 3 Updated 27 August 2008
•PDCO meeting dates 2009 Rev. 2 Updated 26 September 2008

Putting a PIP/waiver together

- Read the guidance available – and ask EMEA if unclear
- Check the approved PIPs/Waivers (+ class waivers)
- Obtain relevant expertise and resources (non-clin, clin, CMC)

After submission

- Be ready at the validation – no fixed timing for questions, and response time is very tight
- Be prepared for clock-stop
- Don’t panic at Day 30 – not yet the Request for Modifications
- At Day 60 ask for a clarification TC – potentially the only chance for a conatct during procedure

Conclusions

- **If you want to file MAA**
  - Approved PIP/waiver mandatory
- **If you want to file new indication/formulation**
  - Approved PIP/waiver mandatory
- **If you want to get reward**
  - compliance with and completion of PIP mandatory
- **If you want to obtain the most of the opportunities**
  - have strategy in place on time!

Thank you