Regulatory strategy: PIP Modifications

Paolo Tomasi M.D. Ph.D.

Head of Section, Paediatric Medicines
Human Medicines Special Areas
European Medicines Agency

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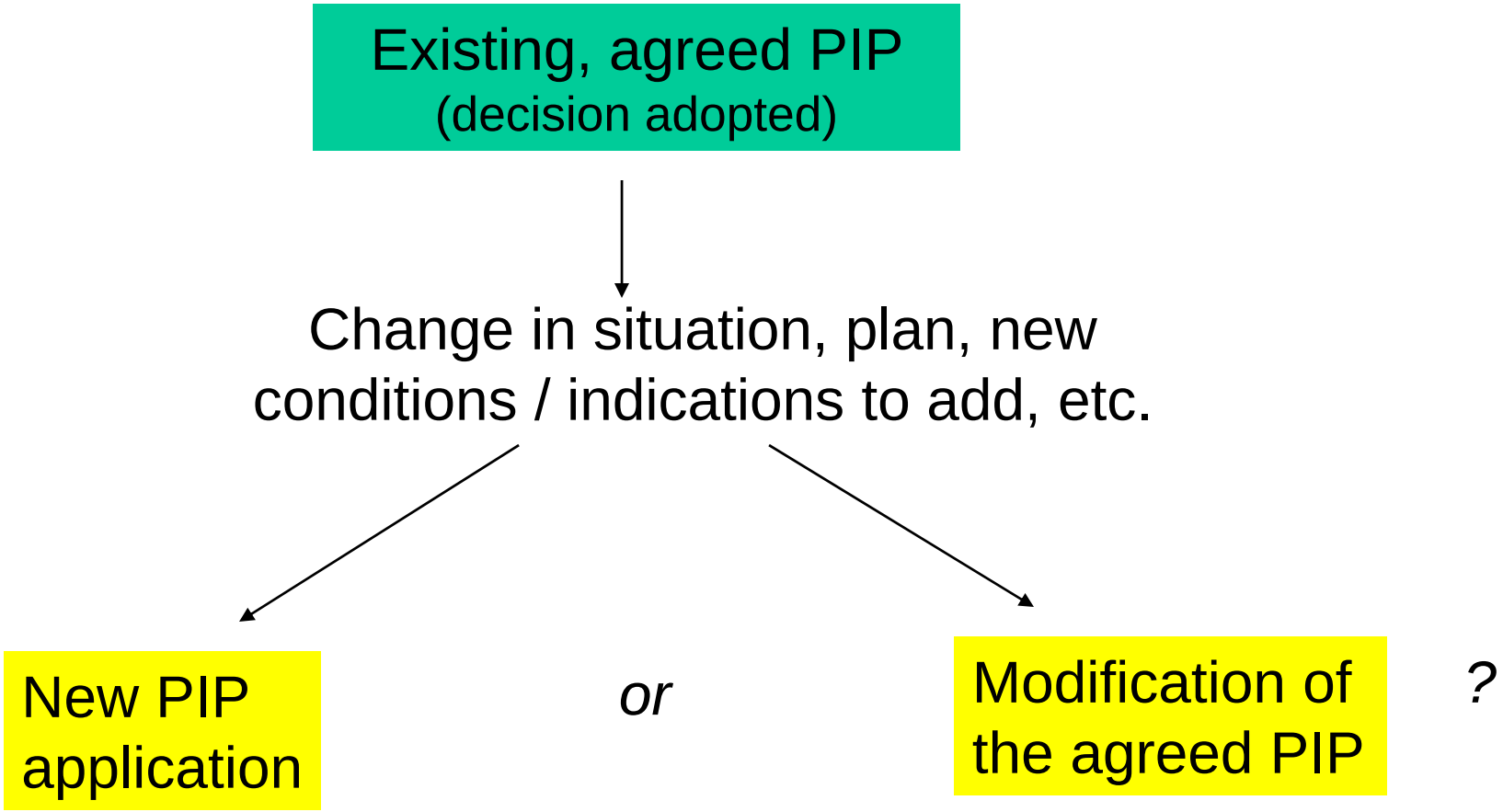
Modification of an agreed PIP, or new PIP?



Modification of an agreed PIP, or new PIP?

2 principles:

1. All conditions / indications under simultaneous development must be discussed in the same PIP application/opinion *(EU Commission guideline)*

2. At the time of the application for marketing authorisation / variation / line extension, all the conditions/indications being applied for in a single market authorisation / variation / line extension must be included in a single PIP

Modification of an agreed PIP, or new PIP?

Therefore:

1. If two (or more) conditions / indications are being developed at different times, **and** they will be included in separate regulatory applications, a new PIP may be requested

2. If the conditions / indications are being developed at the same time, **or** there will be a single regulatory application for all of them, a request of modification of an agreed PIP shall be submitted

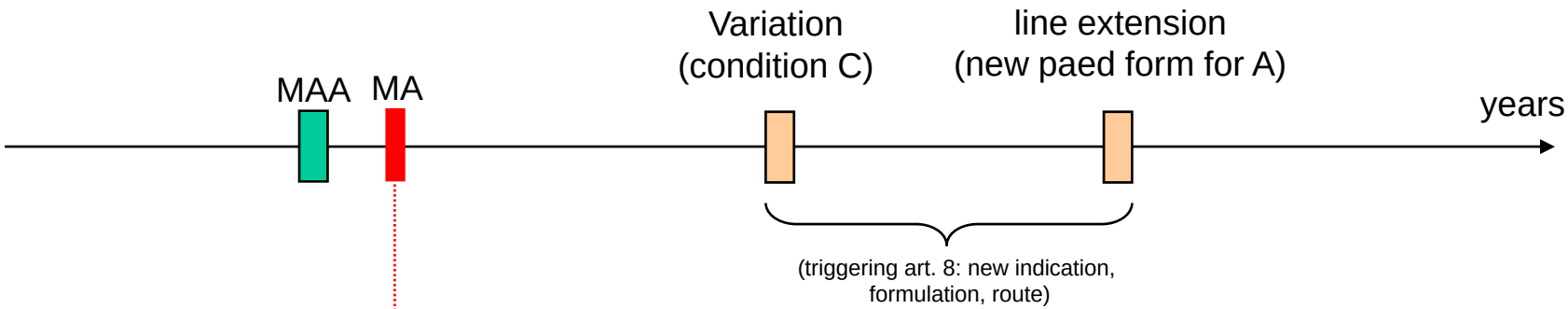
Modification of an agreed PIP, or new PIP?

Rationale of a further PIP application:
To avoid a never-ending PIP for products with multiple, serial conditions/indications, when the total development time might exceed patent/SPC life (no reward)

Reward: 
Is awarded only once, for completion of the “first PIP” agreed

Obligations: 
Are present for every single PIP, not just the first

Modification of an agreed PIP, or new PIP?



Art. 7

PIP 1, conditions A and B

Art. 8

PIP 2, indication in condition C

Second PIP is after MA → art. 8, therefore existing and new indications must be discussed: A, B, and C

First completion of one of multiple PIPs does not necessarily enable reward

Completion of the first PIP that was <u>agreed</u> will enable reward
(if:
- Positive CC
- SmPC modified
- Marketed in 27 MS)

Modification of an agreed PIP

Paediatric Regulation (art. 22):
If, following the decision agreeing the paediatric investigation plan, the applicant encounters such difficulties with its implementation as to render the plan unworkable or no longer appropriate, the applicant may propose changes or request a deferral or a waiver, based on detailed grounds, to the Paediatric Committee.
(omissis)

Modification of an agreed PIP

General considerations:

- Preferably prospective and not *a posteriori*
- 30 or 60 days procedure
- Evaluation team: EMEA Paediatric Coordinator, PDCO rapporteur, PDCO Peer Reviewer
- New waivers / new deferrals may be requested
- Multiple modifications possible, when justified

Procedure for modification of an agreed PIP

Letter of intent 2 months in advance if possible

Submit according to deadlines

Documents to submit:

- Request form
- New part A
- New scientific document (B-E), *only for the modified parts*

European Medicines Agency
Pre-authorisation Evaluation of Medicines for Human Use

REQUEST FOR MODIFICATION OF AN AGREED PAEDIATRIC INVESTIGATION PLAN

1 Please add some information relevant to this application

EMEA (agreed) PIP number: Date of the latest EMEA decision(s) on the PIP:

EMEA decision number:

A copy of the EMEA decision should be annexed

2 Reasons for applying for a modification of the EMEA decision

(Please provide the main reasons in the table below [ref. Art. 22]. The detailed scientific justification should be provided in the relevant documentation. Tick all that apply.)

Is the modification required for administrative changes?
☐ Yes ☐ No

Is the modification required for changes in either measures or timelines as stated in annex I of the decision?
☐ Yes ☐ No

If yes, please specify:

☐ **Changes in the timelines as stated in annex I of the Decision**

☐ **Changes in the measures as stated in annex I of the Decision, specified as follows:**

☐ New/changed **WAIVER request** (tick all that apply)
- ☐ New/changed **condition**
- ☐ Change in **subset(s) of the paediatric population, pharmaceutical form(s) and route(s) of administration covered**

☐ Modification of the **PAEDIATRIC INVESTIGATION PLAN** (tick all that apply)
- ☐ Modification of **indication to be investigated**
- ☐ Modification of **subset(s) covered**
- ☐ Change in **formulation(s)**
- ☐ Modification of key binding elements (not time lines) of **studies/measures**

Procedure for modification of an agreed PIP

3 Please provide a list of the modification(s) of the measures and timelines as stated in the annex 1 of the Decision *(only include measures/timelines to be modified; add more lines in the table, if necessary)*

Current key binding element	**Proposed change(s)**	**Justification for change (max. 250 words)** *(include number of section in the scientific documentation)*

4 Please specify which part(s) of the scientific documentation have been modified and are submitted (Parts B to F)

Part B; please specify the relevant sections
Part C; please specify the relevant sections
Part D; please specify the relevant sections
Part E; please specify the relevant sections
Part F

Modifications must be justified!

Procedure for modification of an agreed PIP

Procedural steps:

- No formal validation: if application is incomplete / insufficiently justified, risk of negative opinion
- Clarifications and interactions after D30 Summary Report. However opinion at D30 possible
- Opinion adopted: positive even if only one of the modifications requested has been accepted
- New opinion supersedes and replaces previous opinion and contains all key binding elements, not just those modified
- Opinion and decision process is the same as for original opinion (EMEA decision; re-examination possible).

Modifications of agreed PIPs

Meeting highlights from the Paediatric Committee held by written procedure, 19-21 August 2009

Number of Paediatric Committee (PDCO) opinions	**2007**	**2008**	**2009**	**Cumulative total**
Positive on full waiver	10	48	46	104
Positive on PIP, including potential deferral	2	81	93	176
Negative opinions adopted	0	4	9	13
Positive opinions adopted on modification of a PIP	**0**	**8**	**22**	**30**
Positive opinions on compliance with a PIP	0	5	5	10
Negative opinions on compliance with a PIP	0	0	1	1

Quiz!

PaediaDrugs GmbH has an agreed PIP for condition A, with a completion date December 2014. However results in adults suggest a new study in condition B, scheduled to terminate in January 2015. MAA for both is foreseen for July 2015. The company should:

a) Request a modification of the agreed PIP
b) Present a new PIP application for condition B
c) Either a) or b) are possible
d) Do nothing, as neither is necessary

Quiz!

Kidpharm Inc. has an agreed PIP for two conditions (A and B), with a completion date for studies in both conditions in December 2014. However, due to recruitment problems, the study For condition B is now scheduled to terminate in February 2016. The company should:

a) Request a modification of the agreed PIP
b) Present a new PIP application for condition B
c) Either a) or b) are possible
d) Do nothing, as neither is necessary

Quiz!

Multipharma Ltd. has an agreed PIP for condition A, with a completion date in December 2014.
However, in January 2014 a new condition B emerges due to interesting results in adults;
the study for condition B is scheduled to terminate in February 2016. MAA for condition A is foreseen for July 2015, and the line extension for condition B in August 2016.
The company should:

a) Request a modification of the agreed PIP
b) Present a new PIP application for condition B
c) Either a) or b) are possible
d) Do nothing, as neither is necessary

I need more help!

EMEA procedural advice

European Medicines Agency - Human Medicines - Medicines for children - Paediatric investigation - Microsoft Internet Explorer

http://www.emea.europa.eu/htms/human/paediatrics/pips_procedural.htm

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- Introduction
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  - Paediatric-use marketing authorisations (PUMAs)
  - Compliance
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- Opinions and decisions on PIP applications
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  - Scientific guidance
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  - Presentations
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- Global cooperation
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Medicines for children — A brighter future for child health

Guidance for applicants

Paediatric investigation plans (PIPs), waivers and modifications - Procedural Advice

This procedural advice addresses a number of questions which applicants may have before submitting an application. The information provided - under the form of Questions and Answers - will be expanded or reviewed progressively, and will be marked by NEW or "Rev." upon publication.

Please consult this procedural advice, the EC "PIP Guideline" (available online at http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:C:2008:243:0001:0012:EN:PDF and the Frequently Asked Questions document (available online at http://www.emea.europa.eu/pdfs/human/paediatrics/52008506en.pdf), before sending a request for further information.

If you need further information on the content, please do not hesitate to contact the Paediatric Team at Paediatrics@emea.europa.eu.

When sections applying to the electronic submission of documents and the template form are amended, the modifications are expected to be reflected in submissions of applications/request for modifications/modifications of PIPs, starting from 3 months after the date of the amendments.

Click on the following questions to see the procedural advice, or alternatively the whole Q&A document can be visualized.

Questions addressed in the Q&A document:

#	Question	Applicable from	Date of last revision
1	How and when should I submit a PIP/waiver Letter of Intent?	current	March 2008
2	When should I submit the application for a PIP and /or Waiver?	current	October 2007
3	To whom should I submit the PIP/waiver application?	current	October 2007
4	How many copies should I submit for a PIP/waiver application?	current	March 2008
5	What information should be provided in the cover letter accompanying the application?	current	October 2007
6	What are the technical requirements for the electronic submission of PIP/waiver applications?	June 2008	March 2008
7	How do I use the electronic template for the PIP/ waiver application (part A)?	current	October 2007
8	What information should I include in the electronic template for PIP/waiver applications (Part A)?	current	October 2007
9	How should I present the scientific documentation (parts B to F)?	June 2008	March 2008
10	What shall I submit if my product falls in a condition listed in the EMEA decision on class waivers?	current	March 2008
11	Should I submit a separate PIP/waiver application in case of duplicate marketing authorisations/marketing authorisation applications?	current	March 2008

http://www.emea.europa.eu/home.htm — Local intranet

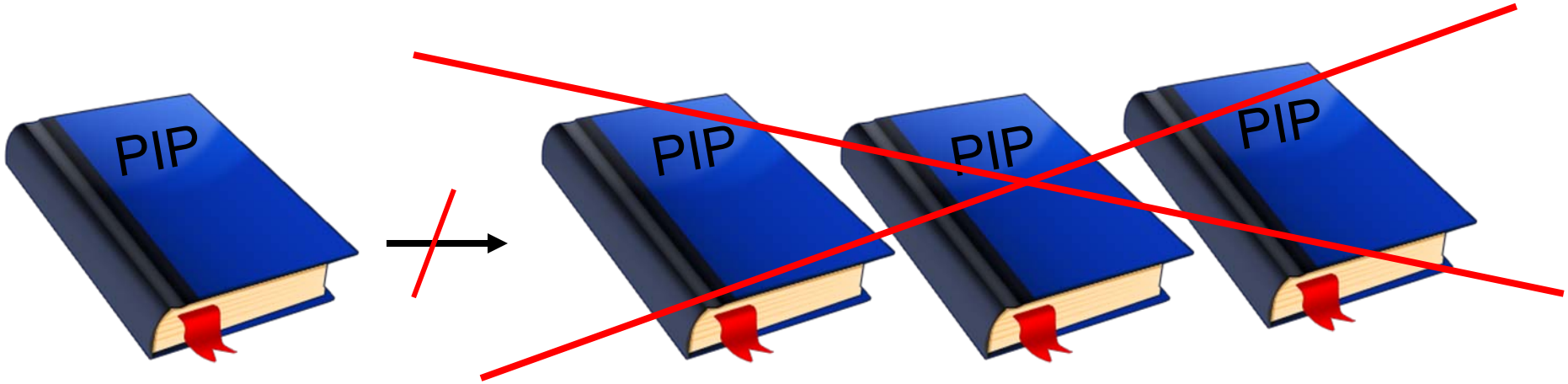
Conclusion

If two (or more) conditions / indications are being developed at different times, **and** they will be included in separate regulatory applications, a new PIP **may** be requested

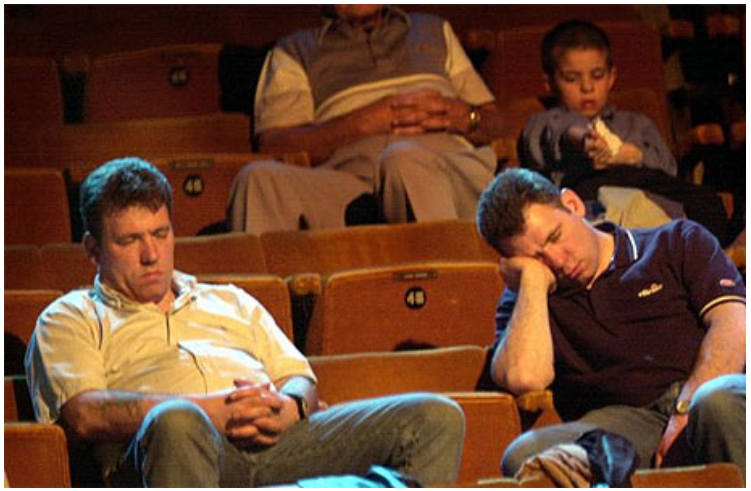
If the conditions / indications are being developed at the same time, **or** there will be a single regulatory application for all of them, a request of modification of an agreed PIP shall be submitted

No more duplicate PIP applications!

- To be published soon in procedural advice (website)
- Applies both to art. 7 and art. 8 applications
- Applies both to informed consent and duplicate MA
- Ongoing products: option to withdraw the duplicates or maintain them.

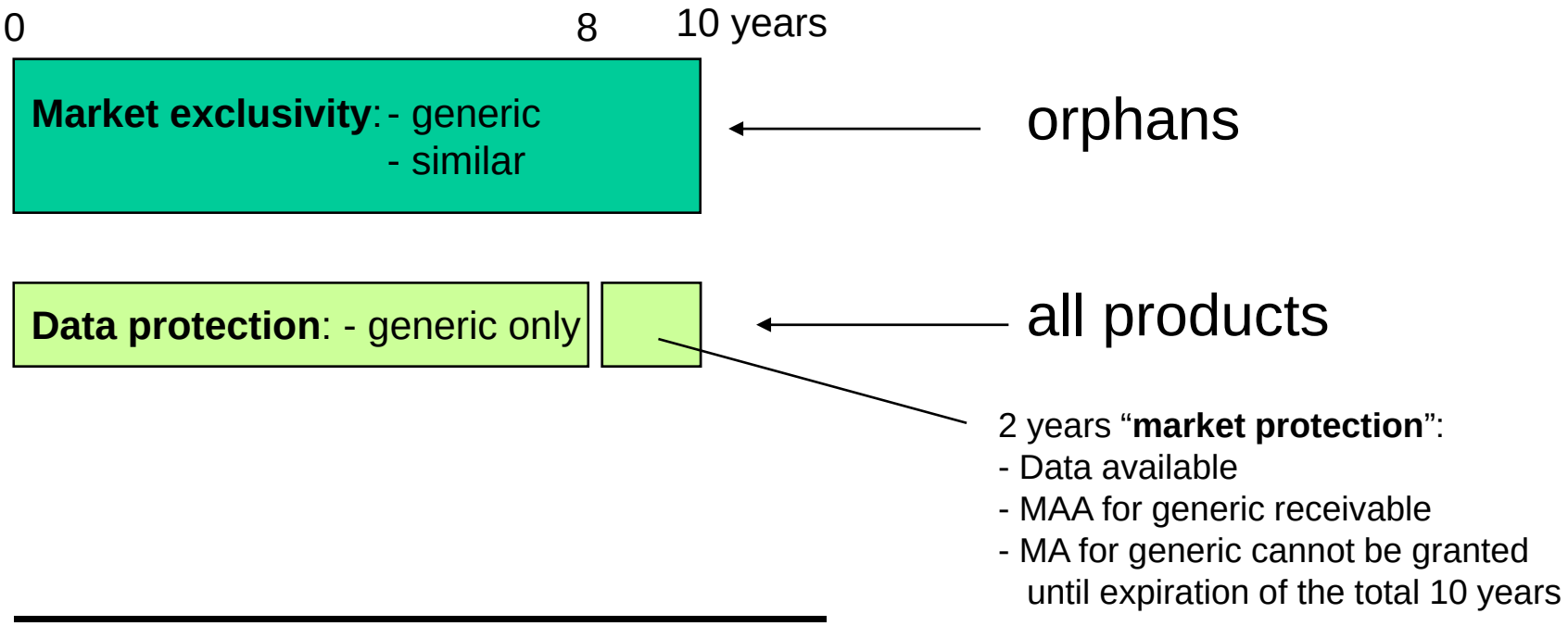


Thanks for your patience



on this very interesting topic

Data protection vs. reward



Paediatric reward:

There has to be a SPC (SPC is prolonged, not patent)