Belgian **F**ederal **A**gency for **M**edicines and **H**ealth **P**roducts
(FAMHP)

Excipients: case study on propylene glycol

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Disclaimer

The views and opinions expressed in the following PowerPoint slides are those of the individual presenter and should not be attributed to the Belgian Federal Agency for Medicines and Health Products or the European Medicines Agency.

PG: case study

D30 (March 2008):

- 8 mg PG/mL w/v Solution for **iv Infusion.**
- **Short-term** treatment when administration by intravenous route is clinically justified by an urgent need to treat or when other routes of administration are not possible.
- The company proposed to treat children from **term neonates to adolescents.**
- **Preterm neonates are not included!**
- **REFLECTION PAPER: FORMULATIONS OF CHOICE FOR THE PAEDIATRIC POPULATION (**EMEA/CHMP/PEG/194810/2005).

Products containing high levels of propylene glycol **should not be administered to paediatric patients below the age of 4 years.** Main toxic action is depression of the central nervous system.

PG: case study

Safety concerns:

- **ADME:**
  - Excretion: **in adults** about 45% renal clearance, rest metabolic clearance
  - **In children**:
    - Limited metabolic clearance below **five years** of age (ADH, alcohol dehydrogenase, but also aldehyde dehydrogenase)
    - Low glomerulare filtration rate in neonates. Adult levels of GFR are reached between 1 and 2 years of age (CPMP/PEG/35132/03, DISCUSSION PAPER ON THE IMPACT OF RENAL IMMATURITY WHEN INVESTIGATING MEDICINAL PRODUCTS INTENDED FOR PAEDIATRIC USE).

PG: case study

Safety concerns:

- **ADME:**
- Elimination half life:
  - 2-4h in adults
  - 19h in preterm ≤ 1.5 kg,
  - 8-9h in (near)term
- Safety concerns: longer elimination half-life and potential accumulation
  - CNS depression
  - Lactic acidosis/Hyperosmolarity
  - Renal toxicity (proximal tubules)/liver toxicity …

PG: case study

PIP final opinion :

o **Subset(s) covered:**

From Preterm newborn infants to less than 28 days.

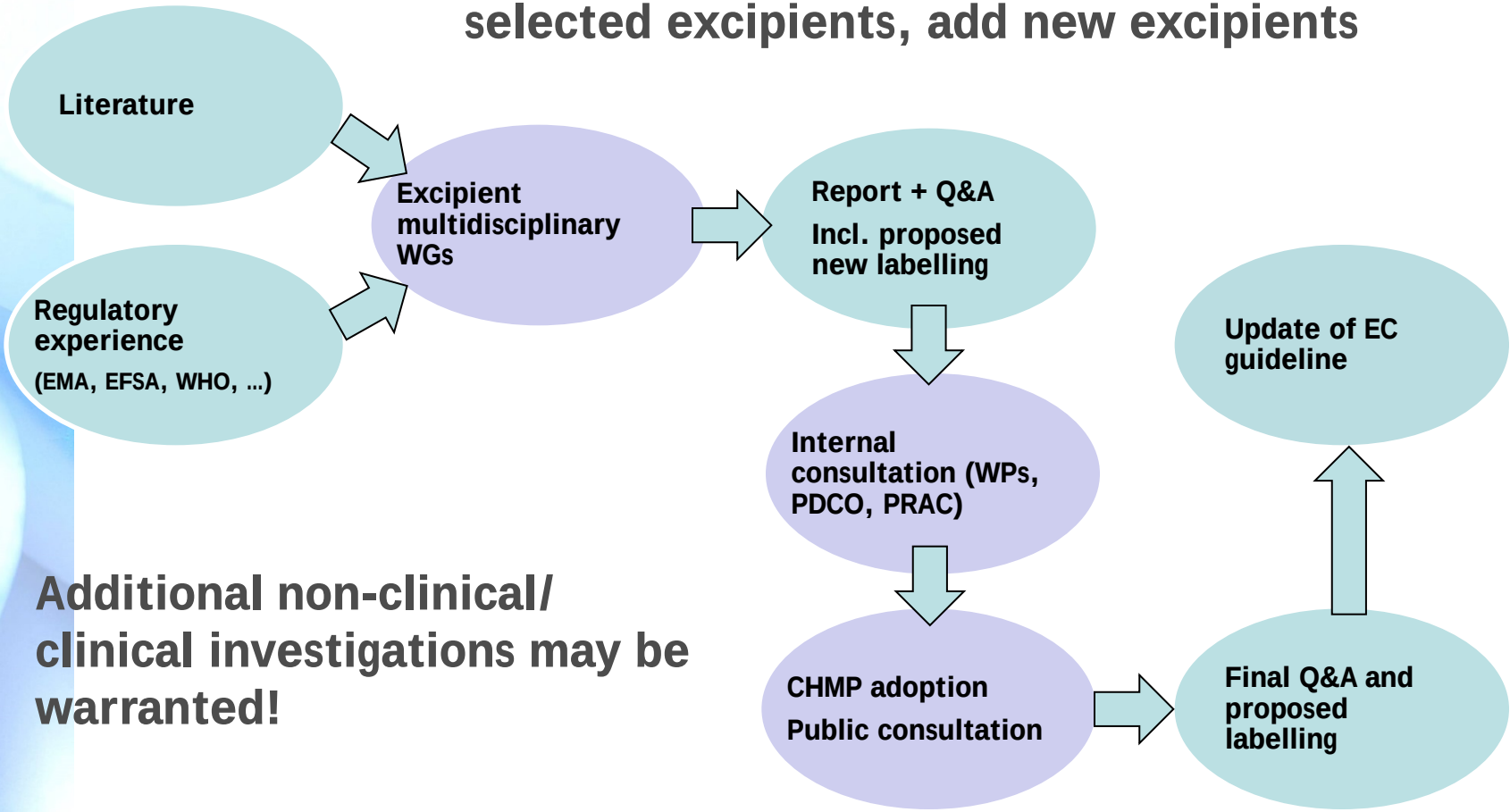
Paediatric study performed in neonates (61 including 24 preterms, 24 - 48 mg/kg/day PG <solution). No safety issues

MA denied because:

- Another formulation without PG was on market
- The neonate study was of short duration, no long-term follow-up, no PG exposure data…

Revision process for each excipient

CHMP Excipients Drafting Group: update the labelling of selected excipients, add new excipients



Additional non-clinical/ clinical investigations may be warranted!

PG Report's conclusion

Permitted daily exposures (PDE): animal data

Species	Rat	Dog	Mouse	Monkey	Juvenile mice
NOAEL for PDE calculation	2000 mg/kg/day	5000 mg/kg/day	10000 mg/kg/day	Insufficient data	1000 mg/kg/day
F1 (extrapolation between species)	5	2	12		12
F2 (variability between individuals)	10	10	10		10
F3 (exposure duration)	1	5	1		10
F4 (severe toxicity) and F5 (no-effect level not established) = 1					
PDE (mg/kg/day)	40	50	83		1

PG Report's conclusion

Animal and clinical data:

Daily dose considered to be safe whatever the duration and the route of administration, with the exception of inhalation. Special attention will have to be taken to avoid local hyperosmolality, CNS, cardiovascular, and/or respiratory effects during bolus parenteral administration.

	neonates up to 28 days (or 44 weeks post menstrual age for pre-terms)	1month (29 days) up to 4 years	5 years up to 17 years and adults
Safety limits	1 mg/kg	50 mg/kg	500 mg/kg

Higher doses may be administered, but will have to be justified and non-clinical and/or clinical studies may have to be designed on a case by case basis in order to support the safety of the proposed formulation.

Some lessons learnt

Generally recognised as safe/well known excipients used outside « safety limits »:

- **Does the same product exists without?**
- **Justify its use**
- **Decrease its concentration as far as possible**
- **Discuss safety risk and safety monitoring**
- **Additional non-clinical/ clinical investigations may be warranted!**

New excipient:

- **Non-clinical development**
- **Toxicity profile should be determined**
- **The need to perform toxicity studies of the product in combination with the excipient should be addressed**
- **Toxicity/PK during clinical studies may be warranted**
- **...**

Thank you for your attention!

CHMP Excipients Drafting Group: General information

1- The excipients drafting group (composition + mandate):

http://www.ema.europa.eu/ema/index.jsp?curl=pages/contacts/CHMP/people_listing_000127.jsp&mid=WC0b01ac0580a02de1

2- Work programme 2016:

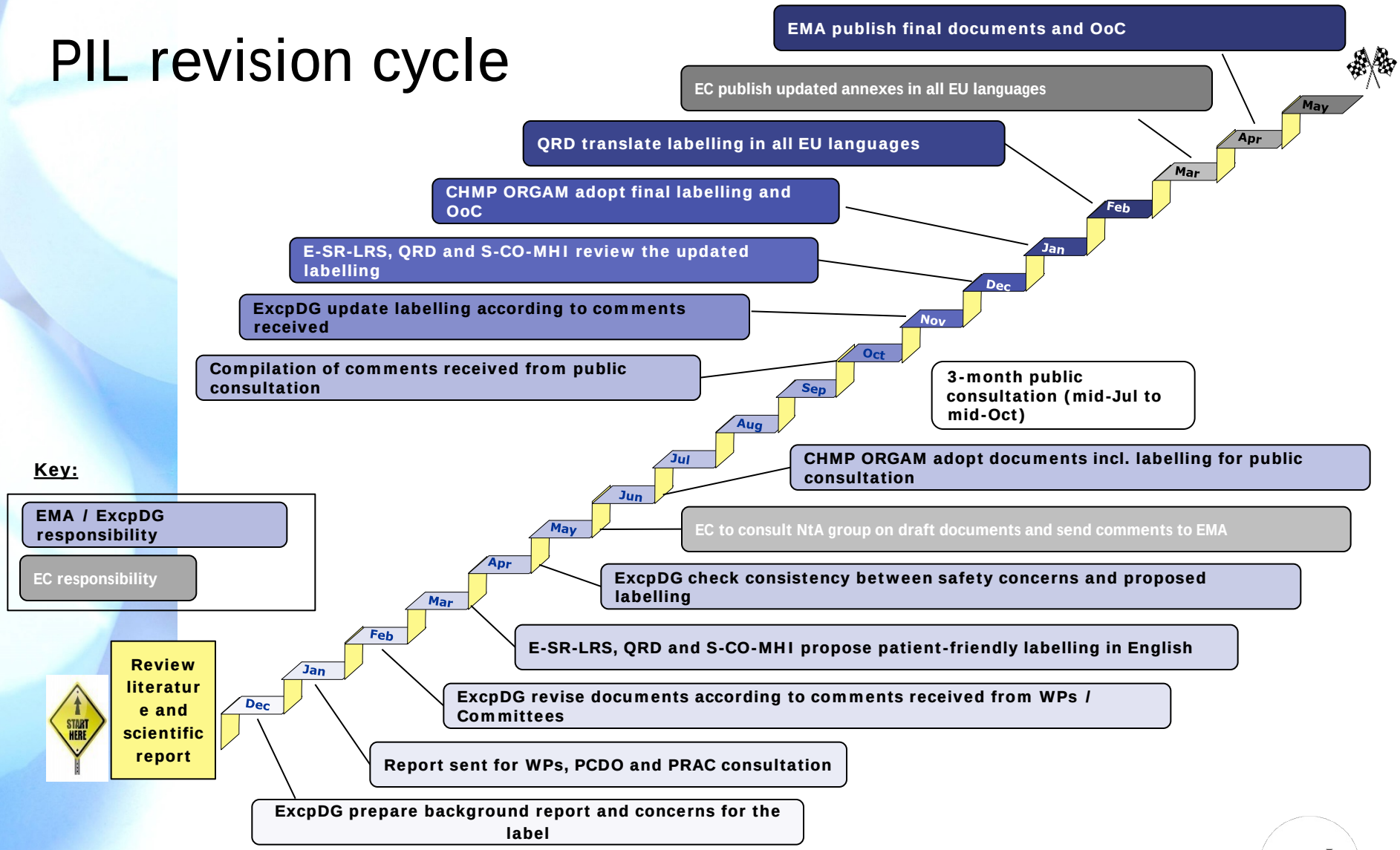
http://www.ema.europa.eu/docs/en_GB/document_library/Other/2016/03/WC500203384.pdf

3- Published excipients are available on EMA website following the path:

www.ema.europa.eu > Human regulatory > Product information > Reference and guidelines > Excipients labelling

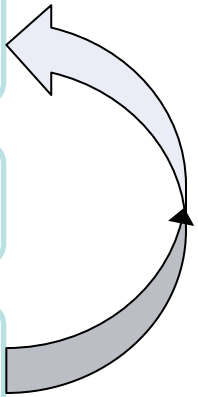
There are currently 3 drafts under public consultation until **3 August 2016: Aspartame, Fragrance allergens, Fructose and Sorbitol**

PIL revision cycle



When to expect updated Annexes

- Core text of the guideline to be finalised after public consultation (Dec-16?)
- Preparation of a first updated Annex with updated/new excipients labelling translated in all EU languages.
- Finalised updated Annex published on the NTA website.
- Publication of final Information for the package leaflet (together with the background report and the overview of comments received during the public consultation) on EMA website.
- Preparation of a second updated Annex.



Documents for CHMP adoption after public consultation

Questions and answers on ethanol in the context of the revision of the guideline on 'Excipients in the label and package leaflet of medicinal products for human use' EMA/CHMP/507988/2013

Action: Final Q&A for adoption in Q2 2016.

Comments: Cooperation with HMPC. Background review document (EMA/CHMP/281628/2013) to

Questions and answers on propylene glycol (EMA/CHMP/704195/2013)

Action: Final Q&A for adoption in Q2 2016.

Comments: Public consultation ended on 28 February 2015. Background review document (EMA/CHMP/334655/2013) to be published with Q&A for information.

Questions and answers on cyclodextrins (EMA/CHMP/495747/2013)

Action: Final Q&A for adoption in Q2 2016.

Comments: Public consultation ended on 28 February 2015. Background review document (EMA/CHMP/333892/2013) to be published with Q&A for information.

Questions and answers on sodium (EMA/CHMP/338679/2014)

Action: Final Q&A for adoption in Q2 2016.

Comments: Public consultation ended on 30 September 2015. Cooperation with PRAC.

Questions and answers on boric acid (EMA/CHMP/619104/2013)

Action: Final Q&A for adoption in Q2 2016.

Comments: Public consultation ended on 3 November 2015. Background review document (EMA/CHMP/765436/2012) to be published with Q&A for information.

Questions and answers on sodium laurylsulfate (EMA/CHMP/606830/2014)

Action: Final Q&A for adoption in Q2 2016.

Comments: Public consultation ended on 3 November 2015. Background review document (EMA/CHMP/351898/2014) to be published with Q&A for information.

Documents to be released for public consultation

Information in the package leaflet for fructose and sorbitol (EMA/CHMP/466886/2014)

Action: Draft to be released for 3-month public consultation in Q1 2016.

Information in the package leaflet for aspartame (EMA/CHMP/134648/2015)

Action: Draft to be released for 3-month public consultation in Q1 2016.

Information in the package leaflet for fragrances (EMA/CHMP/273718/2014)

Action: Draft to be released for 3-month public consultation in Q3 2016.

Information in the package leaflet for dextrans (EMA/CHMP/360711/2014)

Action: Draft to be released for 3-month public consultation in Q3 2016.

Information in the package leaflet for L-proline (EMA/CHMP/332530/2015)

Action: Draft to be released for 3-month public consultation in Q3 2016.

Information in the package leaflet for Lactose (EMA/CHMP/810689/2013)

Action: Draft to be released for 3-month public consultation in Q4 2016.

Information in the package leaflet for polysorbate 80 and 20 (EMA/CHMP/223893/2012)

Action: Draft to be released for 3-month public consultation in Q4 2016.

Information in the package leaflet for Phosphates in eye drops

Action: PL information to be added in the Annex when first published.
Comments: Final Q&A available (ref. EMA/CHMP/753373/2012).