The start of PaedForm - a pan-European Paediatric Formulary

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INTRODUCTION

The formulary will collect together on a pan-European level formulations for extemporaneous preparation currently described in national formularies, or those which are well-established in European countries, and make them freely available. Pharmacists and clinicians will be provided with formulations of appropriate quality to allow preparation when no licensed alternative is available on the market. The project has been launched by the European Committee on Pharmaceuticals and Pharmaceutical Care (CD-P-PH) and the European Pharmacopoeia Commission (for which the EDQM provides the Scientific Secretariat).

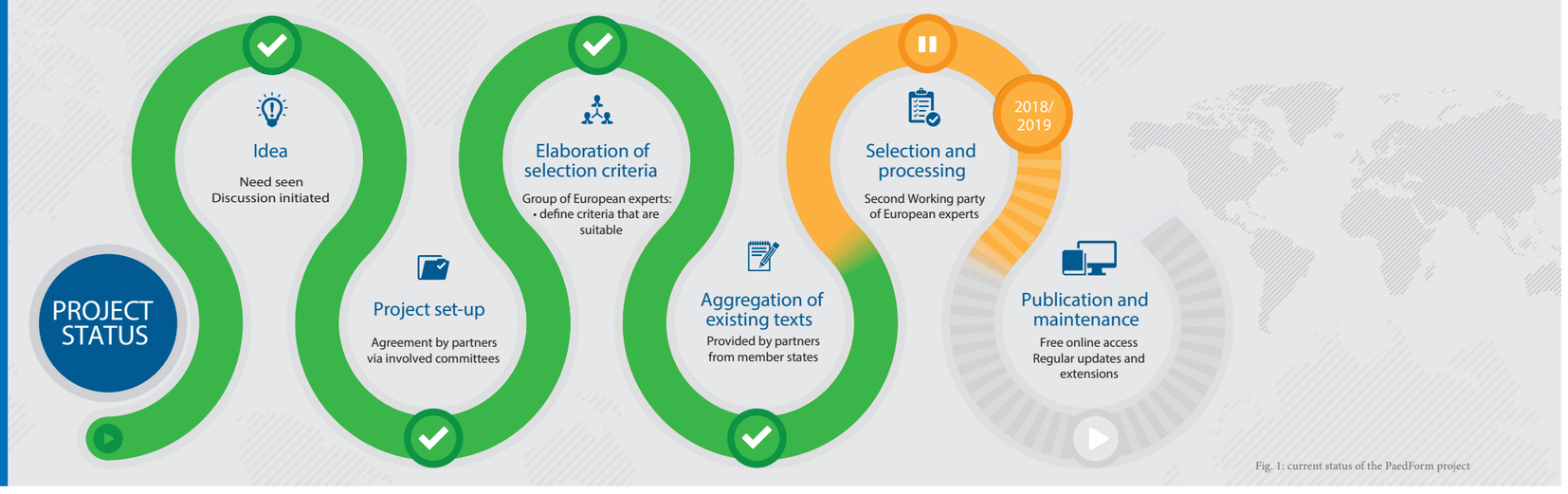

Fig. 1: current status of the PaedForm project

CRITERIA FOR SELECTION OF MONOGRAPHS

Positive assessment for use of active substance including:

- ✓ is **of therapeutic benefit**
- ✓ relevant to current practice
- ✓ **no safety signals**

In addition:

- ✓ **no authorised products** with age-appropriate dosage form available
- ✓ **excipients not harmful**
- ✓ all **excipients** necessary and **suitable** for their intended use
- ✓ active substance and excipients **comply with Ph. Eur.**
- ✓ **evidence on stability**

SELECTED PARTS OF A PAEDFORM MONOGRAPH

Qualitative and quantitative composition

Supplementary information for the compounding pharmacist, e.g. on content of excipients with possible concerns, considerations during development.

Preparation **process** described in a way that ensures **reproducibility**

Suitable tests for **in-process controls**

All available quality control tests given: decision on which to apply for extemporaneous or stock preparation made by compounding pharmacist.

Expiry time: given as in-use and before first opening, if known. Storage conditions and container system are reported.

Source and list of **additional** scientific **references**

DRAFT OF FIRST PILOT PAEDFORM MONOGRAPH

Hydrochlorothiazide 0.5 mg/mL Oral Solution

Route of administration: oral

DEFINITION
1 mL of Hydrochlorothiazide 0.5 mg/mL Oral Solution contains 0.5 mg of Hydrochlorothiazide (Ph. Eur.).
Content: 90.0 to 110.0 (0.45 to 0.55 mg/mL) per cent of the hydrochlorothiazide label claim.
Content of methyl parahydroxybenzoate: 90.0 to 110.0 per cent of the nominal content.
[…]

QUALITATIVE AND QUANTITATIVE COMPOSITION

Composition per 107.7 g (corresponding to 100.0 mL):

Hydrochlorothiazide (Ph. Eur. 0394)	0.050 g
Methyl parahydroxybenzoate	0.077 g
Propylene glycol	0.275 g
Citric acid monohydrate	0.87 g
Disodium phosphate dodecahydrate	0.835 g
Essentia aurantii	0.052 g
Sucrose	20.16 g
Purified water	85.4 g

ADDITIONAL INFORMATION
The formulation contains 2.75 mg of propylene glycol per mL.
The formulation contains 0.77 mg of methyl parahydroxybenzoate per mL.
The concentration of methyl parahydroxybenzoate is lower than 0.1% because of the risk of precipitation, and therefore the storage period is limited to 6 months.
The concentration of 0.5 mg/mL hydrochlorothiazide is the maximum concentration that gives a clear liquid with a limited amount of co-solvent.
Grinding hydrochlorothiazide powder before preparation may shorten the dissolution time during manufacturing.
Hydrochlorothiazide hydrolysis during storage is pH-dependent; it forms salamide and formaldehyde.
The maximum concentration of salamide is limited to 6 per cent, resulting in a negligible concentration of formaldehyde. […]
The pH value is set to 2.5 because of better taste and reduced hydrolysis. […]

PRODUCTION
Ingredients
[…]
Production steps
1. Dissolve citric acid monohydrate and disodium phosphate in 70 g of purified water.
2. Mix sirupus simplex FNA with this solution.
3. Dissolve in this mixture hydrochlorothiazide by heating the solution to 60 °C and stirring.
4. Add methyl parahydroxybenzoate concentrated solution to the warm solution.
5. Cool to room temperature.
6. Add 0.052 g of essentia aurantii.
7. Add purified water to reach a final mass of 107.7 g and mix.

In-Process controls
Appearance: Clear, colourless liquid. Visual observation after steps 3 and 5.
[…]

LABELLING […]

QUALITY CONTROL
Appearance: clear, colourless liquid.
Identification: see assay.
pH (*2.2.3*): 2.5-3.5.
Microbiological purity (*5.1.4*). Complies.
Related substances. Liquid chromatography (*2.2.29*). […]
Assay. Liquid chromatography (*2.2.29*) as described in the test for related substances.
Methyl parahydroxybenzoate. Liquid chromatography (*2.2.29*) as described […]

STORAGE
[…]

REFERENCES
Source: Formulary of Dutch Pharmacists (FNA).
[…]

METHODS AND ONGOING WORK

- The dedicated PaedF working party comprises **17 experts** from hospital pharmacies, academia and national authorities from **14 countries**
- The experts started with **prioritisation** based on paediatric needs published by the EMA Paediatric Committee and criteria for the formulary adopted by the CD-P-PH.
- The **formulations** available for a specific preparation **of high priority will be screened** and a final selection will be made.
- **Draft texts** will be made available by the EDQM **for public consultation** for 3 months (first ones foreseen by the end of 2018).
- The **online formulary** will be **subsequently extended** and regularly reviewed.

RESULTS

- The work on prioritisation is partially complete.
- The first two pilot monographs (**Hydrochlorothiazide** 0.5 mg/mL oral solution and **Sotalol** 20 mg/mL oral solution) are in final drafting stage before public enquiry.
- An explanatory text with general principles will be published together with the 2 monographs.
- 6 additional monographs have been added to the work programme:
  - » **Furosemide** 2mg/mL oral solution
  - » **Azathioprine** oral suspension
  - » **Isoniazide** 10 mg/mL oral solution
  - » **Oxybutynin hydrochloride** 0.25 mg/mL intravesical solution
  - » **Ranitidine** 15 mg/mL oral solution
  - » monograph on an **oral vehicle**.
- Several further monographs will soon be added to the work programme.

CONCLUSIONS

This project is still in its infancy. With the upcoming public enquiry of the first monographs at the end of 2018, it will be visible to a larger audience. With the input of all stakeholders the formulary can in future fulfil its aims: to be an easily accessible, science-based online tool with a collection of child-appropriate formulations that supports its users by promoting the health of children in all countries where no licensed medicine is available.

ACKNOWLEDGEMENTS

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