EMA/FDA/Health Canada workshop on paediatric pulmonary arterial hypertension (PAH)

12-13 June 2017, meeting room 2A
European Medicines Agency, London, United Kingdom
General objectives:

This workshop will bring together experts and stakeholders to discuss requirements for the development of drugs in paediatric PAH and to address the need of the current paediatric clinical practice in a timely manner. The objectives are to:

1. improve the understanding of problems related to the conduct of clinical trials in the paediatric population;
2. refine endpoints and study design to address the clinical trials challenges in this rare paediatric population;
3. set priorities in future research in the field of PK/PD measurements and post-marketing tools in paediatric PAH medicines;
4. provide drug developers with more guidance specific to global product development taking into account current limitations in the development.

Scope

The scope of the workshop is to discuss the current knowledge in the use of medicines in the paediatric population and identify the issues for medicines under development. This applies particularly to aspects related to choice of studies that are relevant and feasible to demonstrate efficacy in the paediatric population where there is still a high unmet medical need.

Who will attend?

The presentations and discussions will include the following experts and impacted stakeholders:

- Regulators: EMA and its scientific committees CHMP, PDCO and PRAC; FDA, Health Canada;
- Academics;
- Clinicians;
- Healthcare professional representatives;
- Patient representatives; and
- Pharmaceutical industry representatives.

Programme committee

**EU network:** Pieter de Graeff (CBG-MEB), Amany El Gazayerly (CBG-MEB), Ninna Gulberg (MPA), Sabine Scherer (BfArM), Clemens Mittmann (BfArM), Marek Migdal (Instytut Pomnik Centrum Zdrowia Dziecka).

**EMA:** Cécile Ollivier, Andreas Kouroumalis, Andrew Thomson, Laura Fregonese, Jan Regnstroem.

**FDA:** Norman Stockbridge, Aliza Thompson, Lynne Yao, Sun Haihao.

**Health Canada:** Allan Aizenman, Ariel Arias, Barbara Njie, Sophie Anne Lamour, Agnes Klein.
Speakers

- Pieter de Graeff: CBG-MEB
- Norman Stockbridge: FDA
- Enrica Alteri: EMA
- Cécile Ollivier: EMA
- Lynne Yao: FDA
- Maurice Beghetti: Centre Hospitalier Universitaire Vaudois
- Gerald Fisher: PAH Europe
- Bruno Flamion: Actelion
- Nazzareno Galié: University of Bologna
- Rolf Berger: University Medical Center Groningen
- Amany El Gazayerly: CBG-MEB
- Daniel Keene: Health Canada
- Christine Garnett: FDA
- Patrik Hassel: PAH sverige
- Valeria Gigante: AIFA
- James Strait: Merck
- Christine Dehn: German Heart Foundation
Workshop programme 12 June 2017

**Chair:** Pieter de Graeff - **Co-Chair:** Norman Stockbridge

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<th>Item</th>
<th>Agenda: Open workshop</th>
<th>Initials</th>
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<tr>
<td>8.45 – 8.55</td>
<td>Welcome and opening.</td>
<td>Enrica Alteri</td>
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<td>8.55 – 9.50</td>
<td><strong>Session 1: Introduction and setting the scene:</strong>&lt;br&gt;Expectation of the day</td>
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<td>This session aims to set the stage for the workshop and discusses the current status (registration status, experiences, and recruitment challenges).</td>
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<tr>
<td>8.55 – 9.15</td>
<td>Global regulatory perspective.</td>
<td>Cécile Ollivier</td>
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<td>9.15 – 9.30</td>
<td>Clinicians perspective.</td>
<td>Maurice Beghetti</td>
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<td>9.40 – 9.50</td>
<td>Industry perspective.</td>
<td>Bruno Flamion</td>
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<td>9.50 – 11.00</td>
<td><strong>Session 2: Clinical perspective</strong></td>
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<td>This session aims to discuss the problems in clinical practice associated with the lack of registered drugs for children and challenges in research.</td>
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<td>9.50 – 10.20</td>
<td><strong>Pulmonary Arterial Hypertension: existing knowledge</strong></td>
<td>Nazzareno Galié</td>
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<td>• Prevalence of different PAH forms in the adult and paediatric population (including PHVD).</td>
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<td>• Diagnosis and natural history of the disease.</td>
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<td>• Comparison of the biological systems response in adult and children for the different class of drugs approved to treat PAH in adults.</td>
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<td>Presentation: 20 mins; Discussion: 10 mins.</td>
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<td>10.20 – 10.50</td>
<td><strong>Management of paediatric patients</strong></td>
<td>Rolf Berger</td>
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<td>• Current standard of care in paediatric PAH and treatment challenges.</td>
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<td>• Clinicians’ expectations from the adult data.</td>
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<td>• Evidence used by clinicians when applying adult PAH drugs in children (PK, PK/PD, clinical trials data and registries).</td>
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<td>Presentation: 20 mins; Discussion: 10 mins.</td>
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<td>10.50 – 11.20</td>
<td><strong>Coffee break.</strong></td>
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<td><strong>11.20 – 13.00</strong></td>
<td><strong>Session 3: Basis for regulatory Decision-Making</strong>&lt;br&gt;Building on Session 2, this session aims to identify the need and requirements for paediatric PAH studies, to discuss current methodological issues related to study design and endpoints.</td>
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<td><strong>11.20 – 11.40</strong></td>
<td><strong>Objectives of paediatric development:</strong>&lt;br&gt;• Target paediatric population and various age groups to be addressed.&lt;br&gt;• PK/PD studies: when we can rely on PK data only or when this needs to be combined with PD data?&lt;br&gt;• Are efficacy studies needed in paediatric PAH – (new vs known MoA).&lt;br&gt;• Study design (including add-on placebo or active control).&lt;br&gt;• Using data from registries.&lt;br&gt;Presentation: 15 mins; Discussion: 5 mins.</td>
<td>Amany El Gazayerly</td>
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<td><strong>11.40 – 12.25</strong></td>
<td><strong>Endpoints:</strong>&lt;br&gt;1. <em>Need for clinical endpoints</em>&lt;br&gt;• Traditional tests and more advanced ones e.g. wearable devices.&lt;br&gt;(10 mins presentation)&lt;br&gt;2. <em>Haemodynamics: invasive vs non-invasive techniques</em>&lt;br&gt;• Properties of PVRI as a surrogate for translation of exercise benefits from adults to children with the same PAH disease spectrum and the same specific intervention.&lt;br&gt;• Is there a place for echocardiography in clinical trials&lt;br&gt;(10 mins presentation)&lt;br&gt;3. <em>PROs and QoL</em>&lt;br&gt;(10 mins presentation)&lt;br&gt;4. <em>Panel discussion</em> (15 mins)</td>
<td>Daniel Keene&lt;br&gt;Christine Garnett&lt;br&gt;Patrik Hassel</td>
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<td><strong>12.25 – 12.45</strong></td>
<td><strong>Use of quantitative tools for study planning purposes and study design optimisation – including registries.</strong>&lt;br&gt;Presentation: 15 mins; Discussion: 5 mins.</td>
<td>Valeria Gigante&lt;br&gt;Andrew Thomson</td>
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<td><strong>12.45 – 13.00</strong></td>
<td><strong>Morning wrap-up</strong></td>
<td>Chair / Co-Chair</td>
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**13.00– 14.00**  
*Lunch break*  

**14.00–16.00**  
**Session 4: Future perspectives on PAH studies in children**  
This section focuses on the minimum clinical information that is needed to submit in order to obtain a MA for PAH in children for drugs already authorised in adults on the basis of earlier discussions.  
Challenges and way forward: recruitment, endpoints across different age groups, long term safety, use of registries, biomarkers.

1. Industry view: Recruitment and feasibility challenges.  
   (15 mins presentation; 5 mins discussion)  
   James Strait
2. Patient/parents view on clinical trials challenges.  
   (10 mins presentation; 5 mins discussion)  
   Christine Dehn
3. Enpr-EMA: Networks’ perspective  
   Mark Turner

General discussion.

**15.45–16.00**  
Closing remarks.  
Chair and Co-Chair

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**Item**  
**Agenda: Regulators only**  

**16.30 – 17.30**  
Regulators debriefing of Day 1.

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**Workshop programme 13 June 2017**

**Item**  
**Agenda: Regulators only**  

**08.30 – 12.00**  
Lessons learnt from recent EMA and FDA procedures.  
Common agreements reached based on last year’s work and workshop discussions.  
Remaining points to be agreed.  
Moving forward.