EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Example for multi-stakeholder collaboration:

Global strategies for pulmonary arterial hypertension (PAH) in children

Acknowledgements: Pieter de Graeff (EMA), Norman Stockbridge (FDA) and Barbara Nije (Health Canada)

Disclaimer

The views expressed in this presentation are those of the speaker and should not necessarily be interpreted as the position of the European Medicines Agency or any of its committees.

Context of development for paediatric PAH medicines

Paediatric PAH: High need to be addressed

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Class of products	Product	PIP	WR*	Authorisation for adults			Authorisation status for children		
				EU	US	Canada	EU	US	Canada
Prostacyclin Analogue	Treprostinil	X		NO	YES	YES	**NO**	**NO**	**NO**
	Selexipag	X		YES	YES	YES	**NO**	**NO**	**NO**
	Treprostinil diethanolamine	X		NO	YES	NO	**NO**	**NO**	**NO**
	Iloprost	N/A		YES	YES	NO	**NO**	**NO**	**NO**
Endothelin Receptors Antagonist (ERAs)	Bosentan	X		YES	YES	YES	PK data	**YES**	PK data
	Ambrisentan	X		YES	YES	YES	**NO**	**NO**	**NO**
	Macitentan	X	WR*	YES	YES	YES	**NO**	**NO**	**NO**
Phosphodiesterase type 5 inhibitor (PDE5 inhibitor)	Sildenafil	X	WR*	YES	YES	YES	**YES**	**NO**	**NO**
	Tadalafil	X	WR*	YES	YES	YES	**NO**	**NO**	**NO**
Guanylate cyclase (sGC) stimulators	Riociguat	X		YES	YES	YES	**NO**	**NO**	**NO**
Vasodilator	Epoprostenol	N/A		YES (NAP*)	YES	YES	**NO**	**NO**	**NO**

* NAP: Nationally authorised product - *WR written Request

What are the hurdles?

1. Clinical and pharmacological hurdles

- Population: rare and heterogeneous
- Medicinal products: high number of competing products
- Gaps in knowledge: pathophysiology, extrapolation, endpoints
- Treatment strategies: from monotherapy to combinations
- Off-label use: is compromising recruitment for paediatric studies and preventing access to the medicines in countries not reimbursing off-label use

What are the hurdles?

2. Regional differences preventing to conduct multiregional paediatric drug development

- Regulatory requirements *(e.g.EMA PIPs and FDA written requests)*
- Operational practicalities *(standards of care, cultural expectations)*
- Patients and families do not want to enrol in any clinical trials *(endpoints, burden of CTs)*

3. Regulator's duty to ensure that medicines for use in children are of high quality, ethically researched and authorised appropriately

- Such an assessment requires clinically robust and relevant data

Addressing the needs

1. Need for global studies

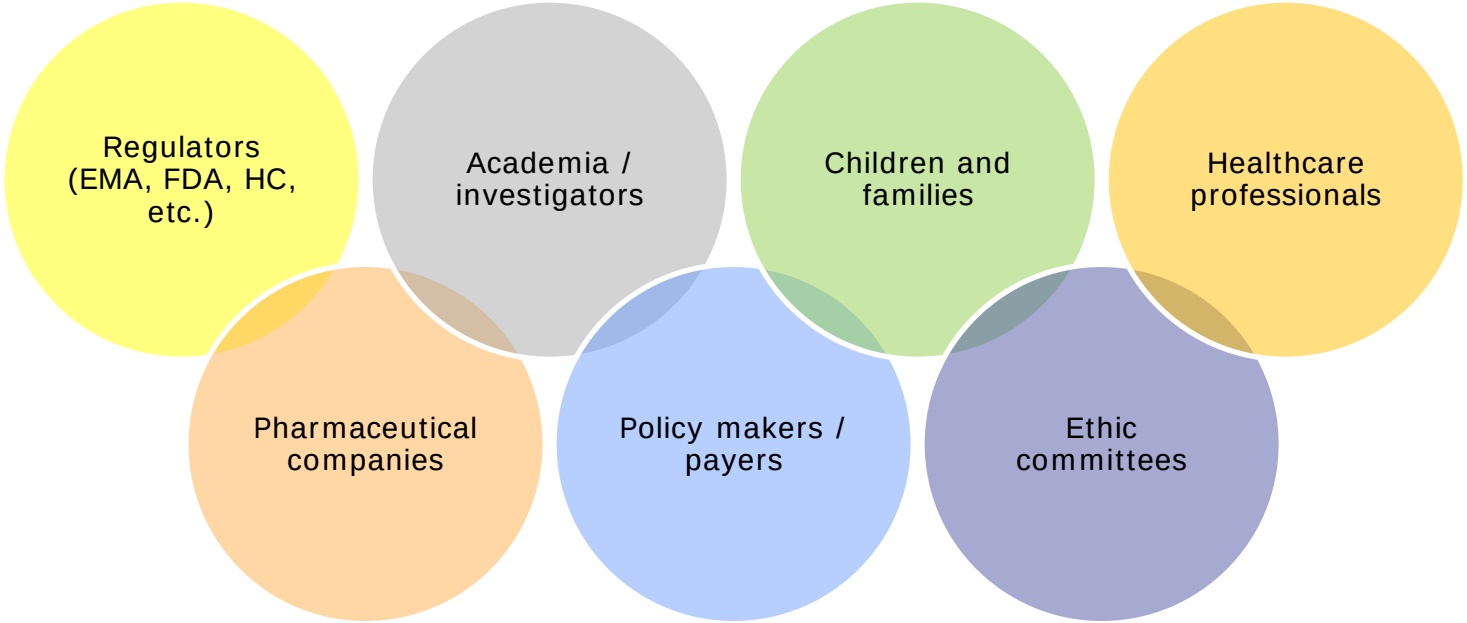
Why?

- Address the feasibility related to small number of patients
- Allocate resources to those areas where studies are most needed
- Better utilisation of scattered (clinical) expertise across territories
- Generate robust and relevant data in a timely manner

How?

- Development and use of paediatric research coordinating centers
- Collaborative studies and data sharing
- Common scientific approach and regulators alignment

2. Global key players driving drug development priorities



3. EMA – FDA – HC paediatric PAH workshop – June 2017

Bridging the clinical practice and regulatory requirements

Meeting objectives:

- To facilitate communication and stimulate collaboration between stakeholders
- To involve **patients in study design**
- To harmonise scientific and regulatory requirements at global level
- To identify gaps in knowledge to be addressed in children with PAH.
- To help ensuring that the data generated will address the scientific questions that are important for licensing in children **in a timely manner**

Building consensus across stakeholders

Workshop preparation with all stakeholders

1. Regulators harmonisation ahead of the workshop
2. Online survey

Why: Lack of consensus within the scientific community

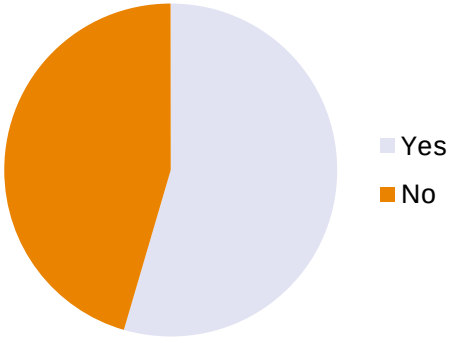
Participants from EU, US, Canada and Japan:

- 22 **Healthcare professionals** treating adult and children with PAH
- 4 **Industry** participants involved in PAH drug development
- 26 **Parents of children with PAH and a child with PAH**

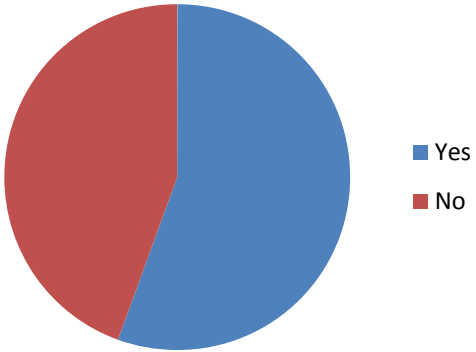
Questions: Pathophysiology, pharmacological behaviour, mechanism of action, extrapolation, endpoints, quality of life and clinical trials

Patients perspective: wake-up call?

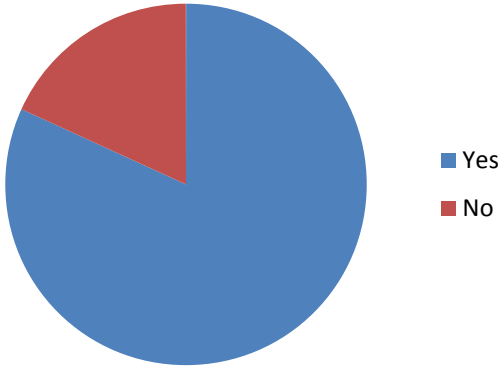
Do you think 6MW test is a good indicator of your child health status?



Would you or your child be willing to participate in a clinical trial?



Are you comfortable having drugs being prescribed off-label? *



* Yes because no other option/ trust my doctor

Meeting outcome: Objectives fulfilled

- **Consensus achieved** for extrapolation, study design and endpoints
- PK/PD randomised dose controlled studies
- Moving towards **echocardiography** (non-invasive endpoint)
- Moving towards **actigraphy** to cover all age groups
- **PROs and QoL** to be developed

Implementing the outcome of the workshop

Action points

1. **Publish the outcome of the workshop** in a peer-review journal with external experts to engage with the community. (regulators, experts, patients and industry involved)

2. Identify on-going activities across stakeholders and **collaborate where appropriate to avoid duplication of efforts**

3. **Product level activities** to be handled under identified regulatory pathways

2. Identify on-going activities across stakeholders and **collaborate where appropriate to avoid duplication of efforts**:

1. **Global need**: Heads of paediatric Clinical Trials Networks in US, Canada and Japan approached
2. Need for a **multi-stakeholders network for paediatric cardiology**
3. **Need from EnprEMA:**

- Support to maintain the dialogue initiated for the PAH workshop between academia, patients, regulators
- Support and offer to share experience in establishing a specialty network (paediatric cardiology)

Conclusion

- **Regulators** have achieved collaboration up to the highest possible level and have developed a multi-stakeholder network
- We are working on facilitating the progress for the development of alternative non-invasive endpoints
- We need the **paediatric cardiology community** to engage and maintain/organise a multi-stakeholder network to address the operational aspects identified as challenging for the conduct of paediatric studies in cardiology
- We need **physician researchers** to continue the rational and critical study of drugs in children through conducting and/or collaborating in well-designed paediatric drug studies

Take home message

Any questions?

Further information

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