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SCIENCE MEDICINES HEALTH

Paediatric Pulmonary Arterial Hypertension (PAH)

Regulators perspective on a Global challenge

EMA – FDA – HC paediatric PAH workshop – 12th June 2017

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Disclaimer

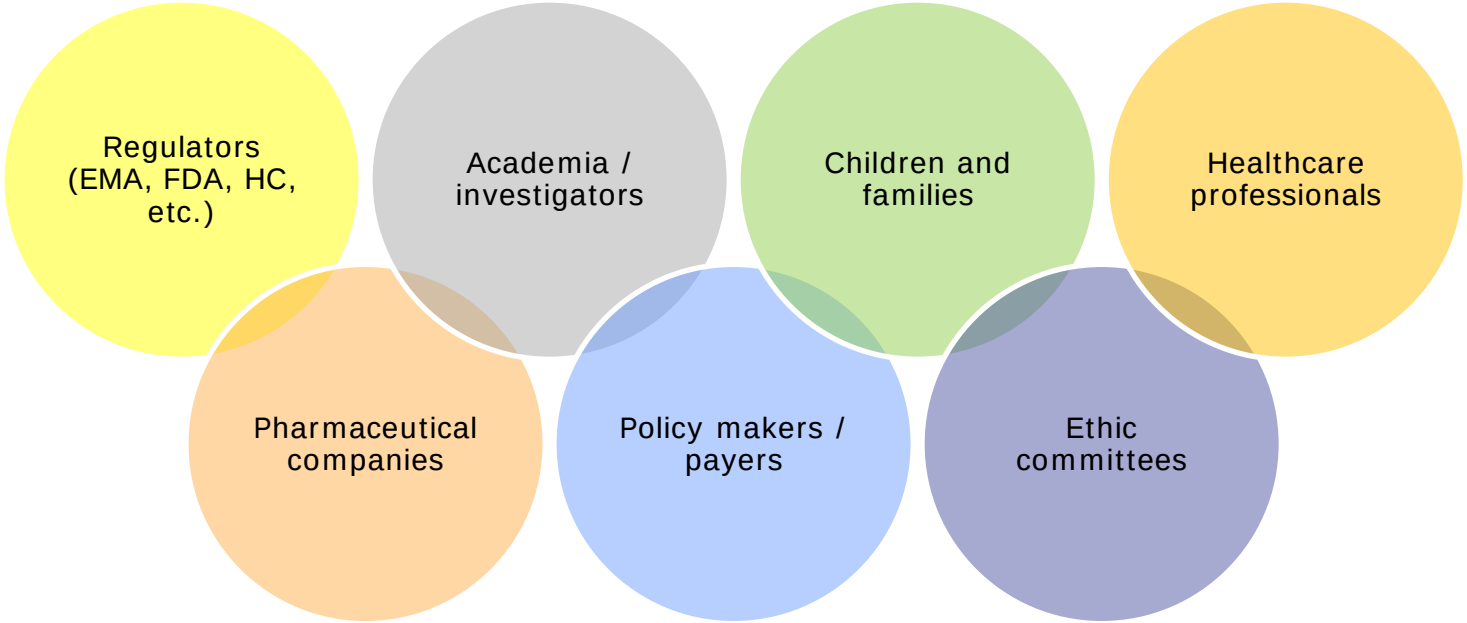
The views expressed in this presentation are those of the speaker and should not necessarily be interpreted as the position of the European Medicines Agency or any of its committees.

Context for development and approval of paediatric medicines

Children are “therapeutic orphans”

- Depending on the country or the age group, 50% to 80% of children are still treated off-label
- Off-label use and lack of well-tested medicines for children have resulted in several major catastrophes
- Regulator’s duty is 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
- Local differences: regulatory requirements, operational practicalities, standards of care, cultural expectations
- Hurdles to conduct multiregional paediatric drug development

Global key players driving drug development priorities



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 (ICH E11 revision)

Paediatric PAH

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	**NO**	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

Context of development for paediatric PAH medicines

- **Population:** rare and heterogeneous
- **Medicinal products**: high number of competing products
- **Gaps in knowledge:** pathophysiology, extrapolation, endpoints
- **Treatment strategies**: from monotherapy to combinations

Online Survey

Why: Lack of consensus within the scientific community

Participants:

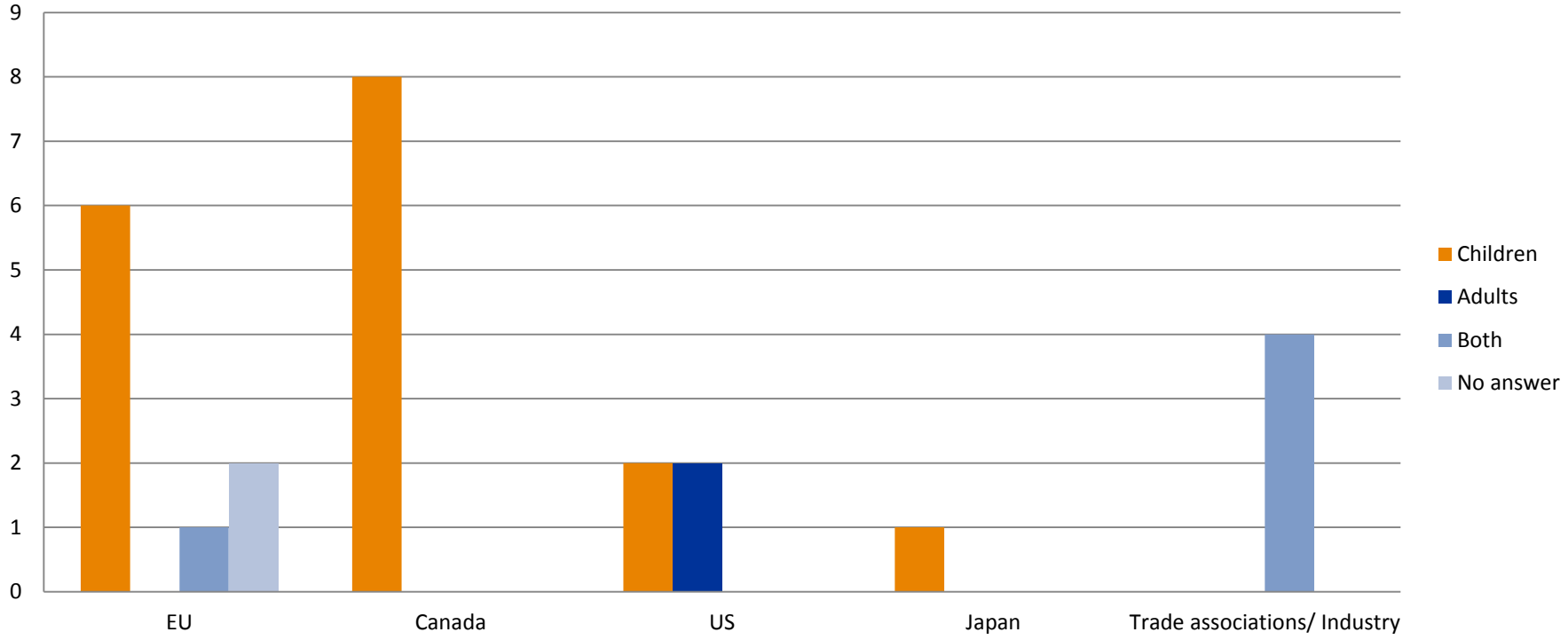
- 22 Healthcare professionals treating adult and children with PAH
- 4 Industry participants involved in PAH drug development
- 26 Parents of children with PAH and a child with PAH

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

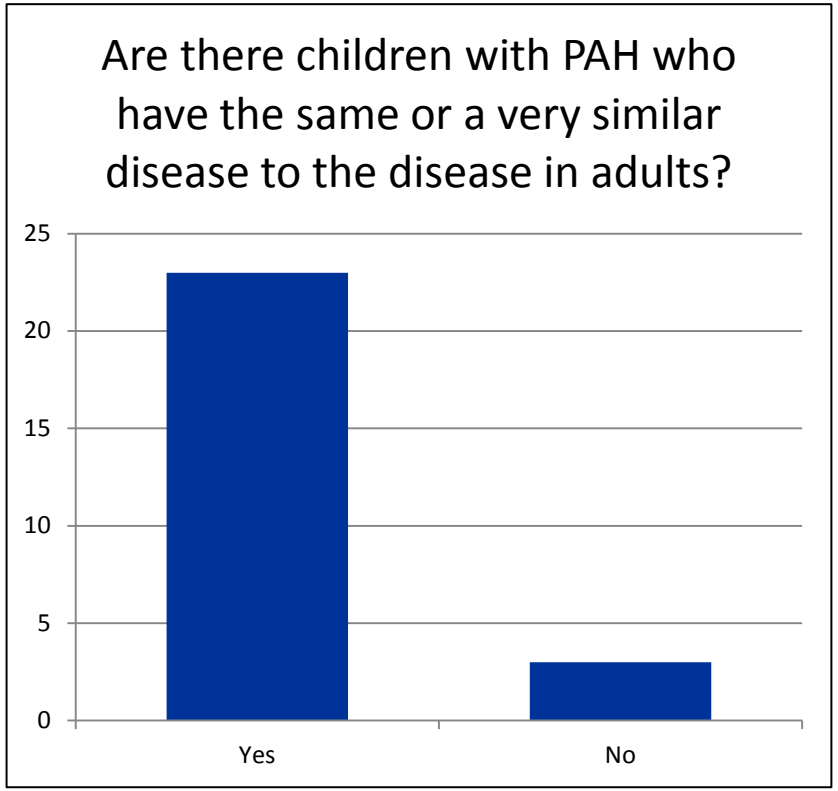
Healthcare professionals

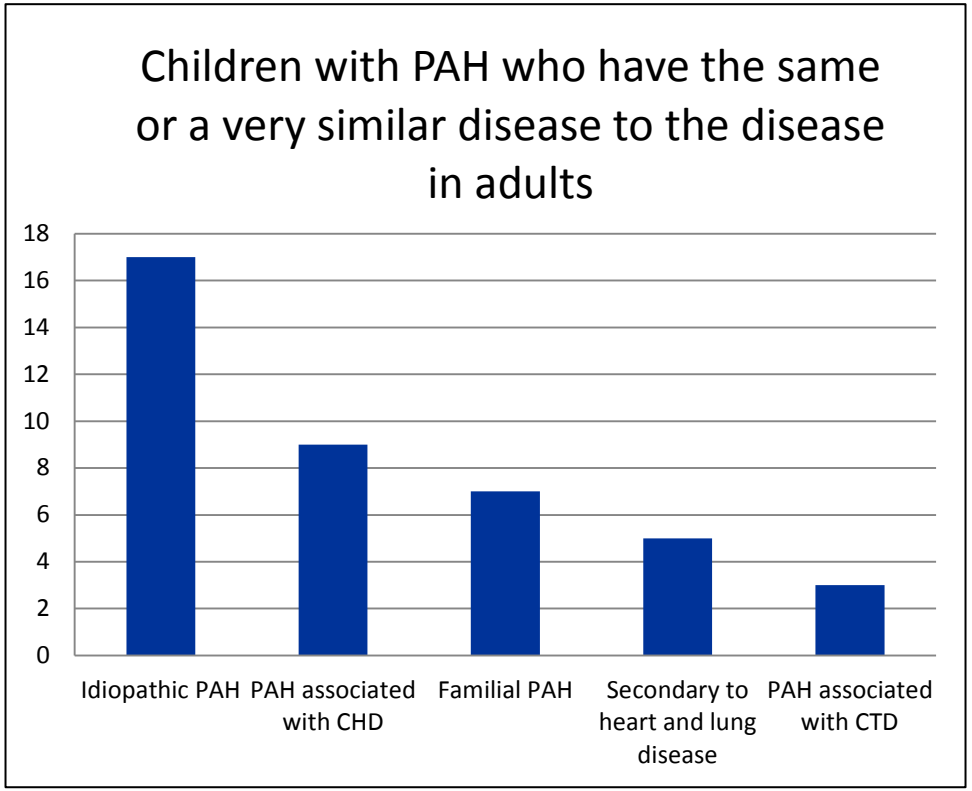
- Clinical and Pharmacological parameters
- Endpoints (6MWT, non-invasive)

HCPs - Online survey response rate

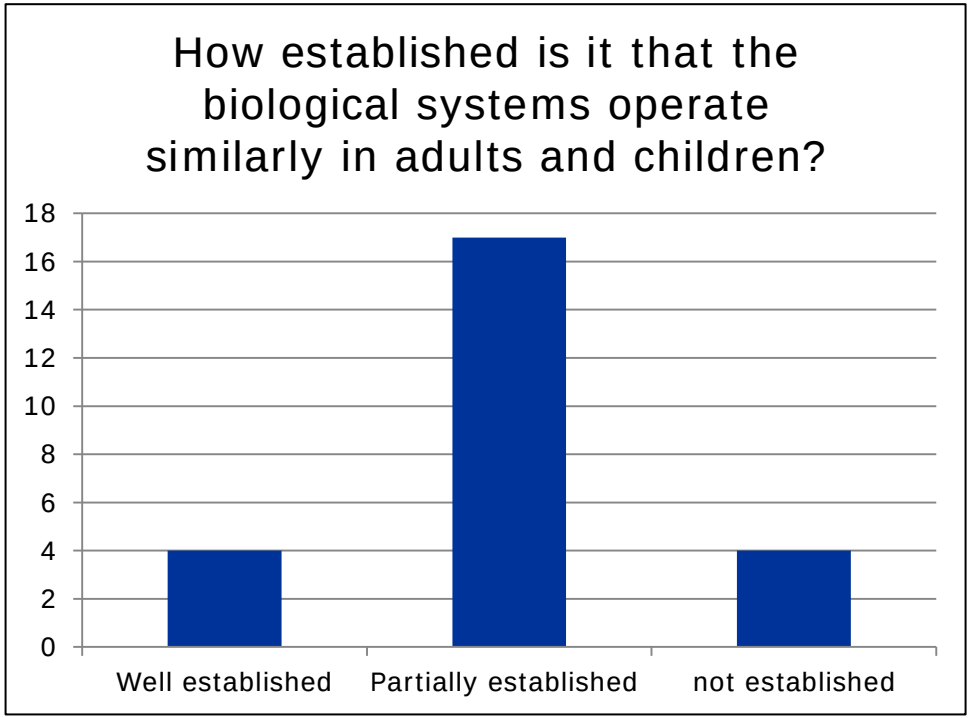


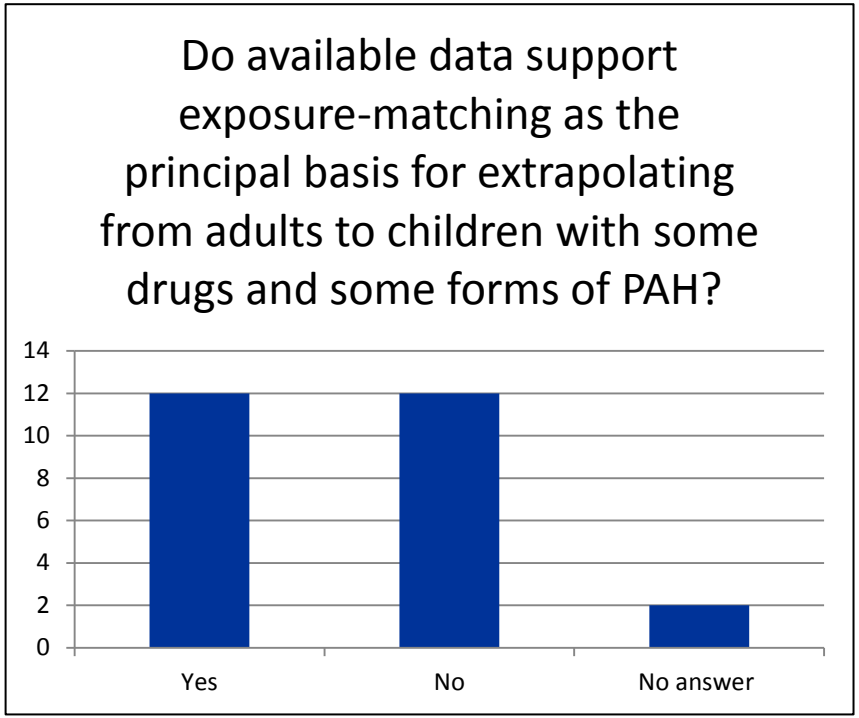
PAH in adults and children – Clinical parameters





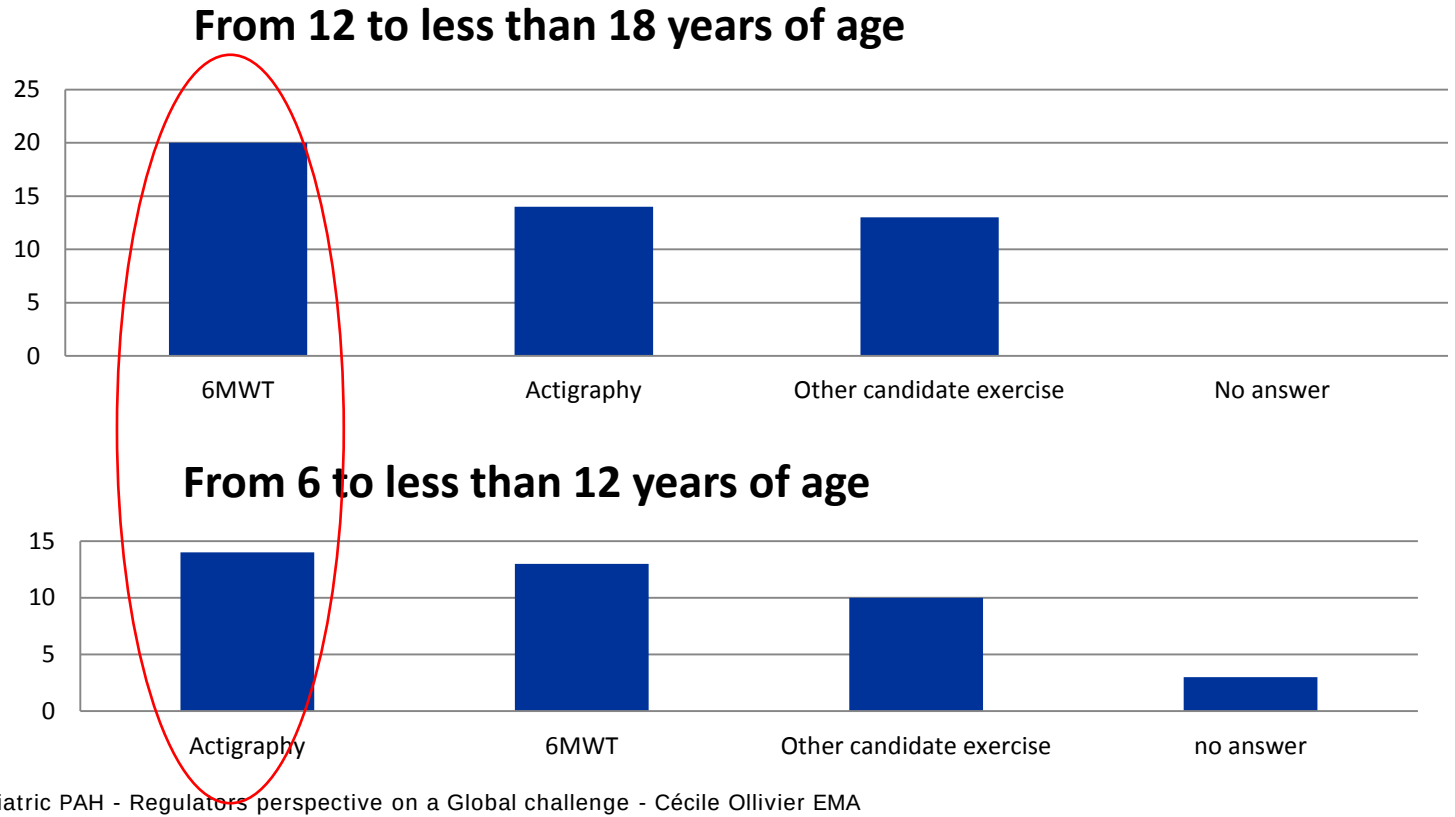
PAH in adults and children – Pharmacological parameters





PAH in children – Endpoints

What endpoints could be used in children:



PAH in children – Endpoints

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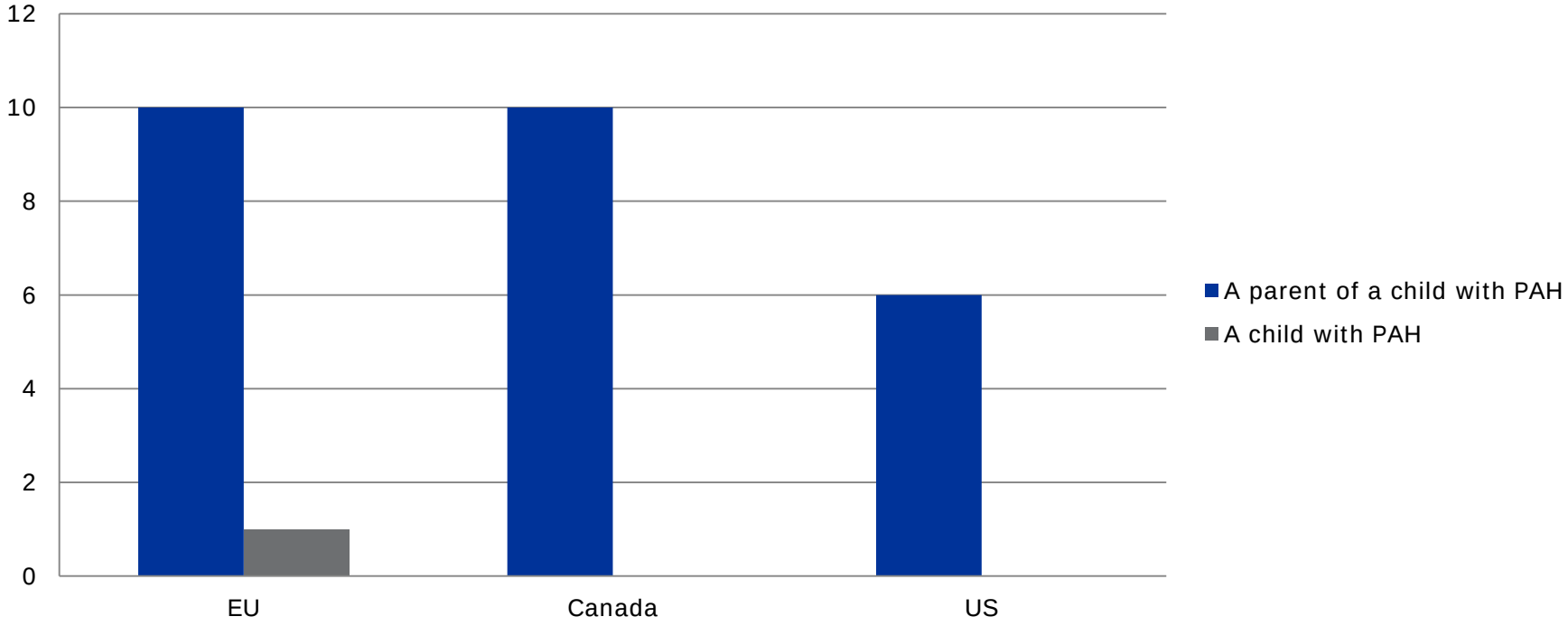
Non-invasive techniques and candidate surrogate markers

Patients

- Off-Label use
- Endpoints
- Daily monitoring
- Clinical trials

Patients - Online survey response



Have you or your child received the following medicinal product?

	Answers
Treprostinil (Tyvaso)	4
Bosentan (Tracleer)	15
Ambrisentan (Volibris)	11
Macitentan (Opsumit)	3
Sildenafil (Revatio)	22
Tadalafil (Adcirca)	12
Riociguat (Adempas)	0
Others?	10
No Answer	0

Do you agree to have drugs being prescribed off-label?

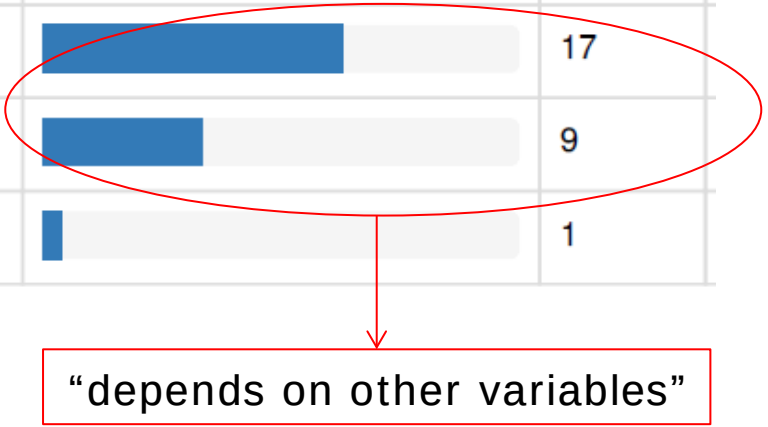
		Answers
Yes		20
No		6
No Answer		1

“We don’t have a choice”

6 Minutes Walk Test – is it a good indicator?

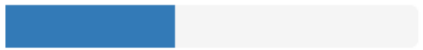
1. If you are familiar with the 6-minute walk test, do you think this test is a good indicator of your child health status?

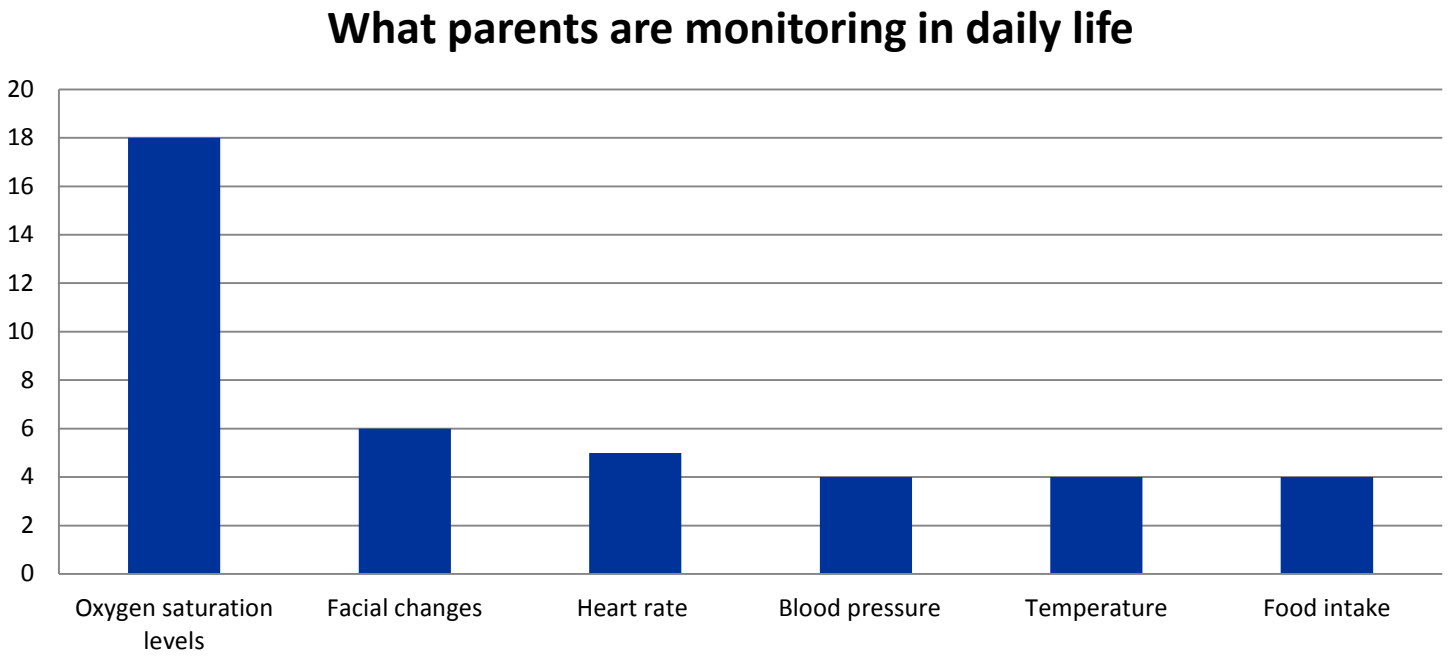
		Answers
Yes		17
No		9
No Answer		1



Signs indicating a worsening of the condition:

2. What are the signs indicating that you or your child's condition is worsening?

		Answers
Decline in daily school attendance over time		9
Decline in daily activities at home over time		13
Significant increase in fatigue		25
Sudden significant decline in overall quality of life		11
Change in physical appearance		18
No Answer		0


What parents are monitoring in daily life
20
18
16
14
12
10
8
6
4
2
0
Oxygen saturation levels
Facial changes
Heart rate
Blood pressure
Temperature
Food intake

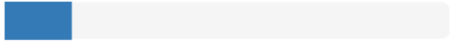
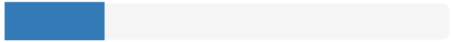
Parents and clinical trials:

If clinical trials have to be conducted to assess if and how the drugs approved for PAH in adults will work in children, would you or your child be willing to participate in a clinical trial?

		Answers
Yes		16
No		8
No Answer		3

“Yes but”

If not, what would be your barriers/concerns?

		Answers
Too risky for me or my child, don't want to test anything that is not already approved for children		3
Risk that me or my child would receive a placebo instead of the new drug		6
Live too far away from a center or do not have the time to go to a center on a regular basis		4
Involves invasive examimations (e.g.:blood samples)		6
I don't have the impression that I'm informed well enough about all risks, advantages and expected outcomes.		5
No Answer		13

Drug developers

Adults developments highlights

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Product	Study Design	Endpoints	Number of patients
Selexipag (Uptravi)	1 study: DB,R,placebo-controlled, parallel groups. (study duration4,2 years)	Time to first occurrence of a morbidity or mortality event up to end of treatment + 6MWD	1,156 patients
Bosentan (Tracleer)	2 studies: R,DB, placebo-controlled	6MWD at 12 weeks for study 1 and 16 weeks for study 2	32 + 213 patients
Ambrisentan (Volibris)	2 studies: DB,R, placebo-controlled	6MWD at 12 weeks	201 + 192
Macitentan (Opsumit)	1 study: DB, placebo-controlled, parallel-group	Time to first occurrence of a morbidity or mortality event, up to the end of double-blind treatment +6MWD	742 patients
Sildenafil (Revatio)	1 study: R, DB, placebo-controlled	6MWD at 12 weeks	278 patients
Tadalafil (Adcirca)	1 study: R, DB, placebo-controlled	6MWD at 16 weeks	405 patients (from 12 years of age)
Riociguat (Adempas)	1 study: R, DB, placebo-controlled	6MWD at 12 weeks	443 patients

Source: EMA EPARs

Paediatric developments highlights

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Product	Original Study design	Initial PIP adoption date
Selexipag (Uptravi)	• DB, R, placebo add-on (S,E,PK) in children from 1 year < 7 year • DB, R, placebo add-on (S,E,PK) in children from 7 year < 18 year	06/2008
Treprostinil diethanolamine	• PK study in children from 1 year < 7 year • PK study in children from 7 year < 18 year • DB,R, multiple dose, placebo add-on (E,S) in children < 8 years of age • Bridging for children > 8 years of age	07/2010
Bosentan (Tracleer) **COMPLETED**	• OL, R, multiple dose (PK, safety) in children from 3 months <12 years	03/2011
Ambrisentan (Volibris)	• OL, R, low and high dose (S,E,PK) in children from 1 year < 7 year • OL, R, low and high dose (S,E,PK) in children from 7 year < 18 year	11/2008
Macitentan (Opsumit)	• DB, R, placebo add-on (S,E,T,PK) in children from 1 month < 7 year • DB, R, placebo add-on (S,E,T,PK) in children from 7 year < 18 year	12/2008
Sildenafil (Revatio) **COMPLETED**	DB,R, placebo, low/medium/high dose (E,S,T) + long term extension	11/2007
Tadalafil (Adcirca)	• OL, PK, S • DB, R, add-on, placebo (E,LT-S)	09/2010
Riociguat (Adempas)	• OL, R, multiple dose (S,T,PK,E)	12/2008
Imatinib (Glivec)	• DB, R, placebo-controlled (PK,PD,S,E)	01/2010
Macitentan/Tadalafil Ambrisentan/Tadalafil	• Full waiver	05/2016 10/2016

Source: EMA PIPs decisions

Paediatric PAH: Paediatric Investigation Plans

- Paediatric developments are disconnected from the adult developments (endpoints/population)
- Different endpoints are necessary for different age groups
- Total number of children to be recruited to complete all the agreed PIPs: 783
- Problems in recruitment leading to significant delays and changes in timelines

What are the hurdles?

Gaps in “belief” between patients, healthcare professionals, regulators, and drug developers

- Healthcare professionals believe that there are still gaps in knowledge that need to be addressed in order to bridge clinical and pharmacological parameters

  Children who respond to short-term vasodilator drug testing have a 5-year survival rate of 90%, whereas children who do not initially respond have a 5-year survival rate of 33%.

- Regulators believe that there are still gaps in knowledge that need to be addressed in order for products to be approved for use in children

  Understanding of the disease in children, drug pharmacology and/or clinical response cannot be quantified yet with sufficient precision

Gaps in “belief” between patients, healthcare professionals, regulators, and drug developers

- Drug developers believe that there are too many differences between regional regulatory requirements/obligations to proceed rationally
  - *EMA PIPs and FDA written requests*

- Patients and families want access to approved therapies but do not want to enrol in any type of clinical trials.

Bridging the gaps: workshop 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**

Bridging the gaps: Points to be addressed today

Population (Session 2):

- Paediatric age groups and subgroups of PAH eligible to be enrolled in studies and when?
- How much can we learn and borrow from the adults development? (integrated strategy)

Endpoints (session 3):

- 6MWT vs actigraphy
- Need for identification and validation of appropriate non-invasive endpoint(s)

Study design (session 3):

- Use of a control (e.g.: placebo), PK/PD/Efficacy/Safety studies considerations

Data:

- Source of existing data from Healthcare professionals and industry (data sharing)
- Prospective planning for post-marketing data collection

Acknowledgements

- EU experts and colleagues
- FDA Programme committee and Lynne Yao
- Health Canada Programme committee and Ariel Arias
- PMDA and Drs. S. Yasukochi and S. Doi of Japanese Society of Pediatric Cardiology and Cardiac Surgery

Thank you for your attention

Further information

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