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Strategic considerations regarding paediatric medicine development – Enpr-EMA reflections

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General Statement

- The Enpr-EMA enables networking and facilitates collaboration through various activities with members from within and outside the European Union (EU), including academia and the pharma industry.
- Enpr-EMA acts as a platform for sharing good practices as well as a pan-European voice for promoting research on medicines for children
- The Enpr-EMA **does not** perform clinical trials or fund studies, or research, or decide on areas for paediatric research
- **Enpr-EMA fully supports the Paediatric Action plan – and it´s 5 elements and building the new EU pharmaceutical strategy – safe and affordable medicines.**

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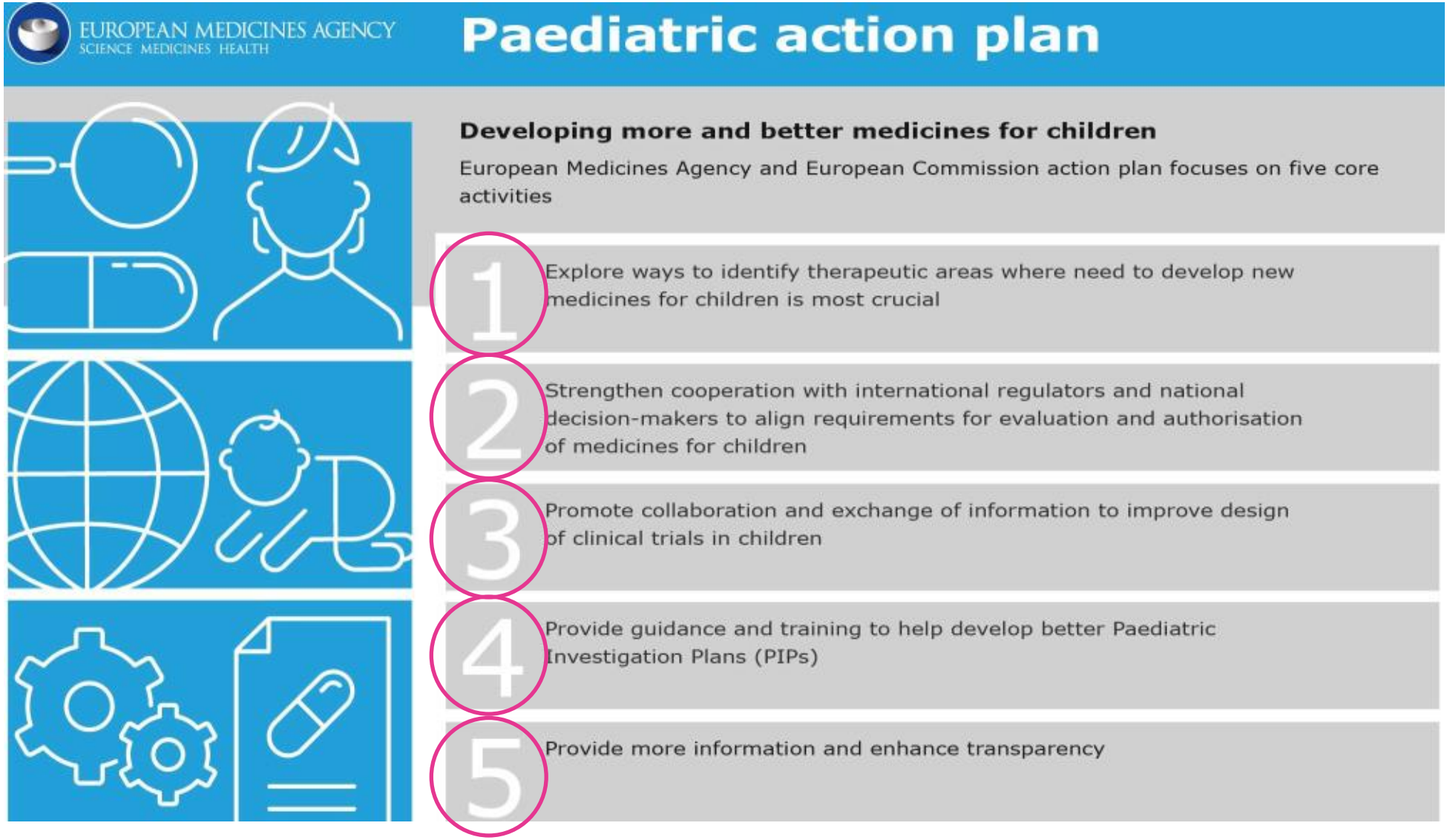
Paediatric Action Plan (2020)



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Enpr-EMA and Research Networks position

R&D

Expertise

MA

Marketed

From laboratory to patient:
the journey of a medicine
assessed by EMA

Research Networks

PIP assessment by the PDCO at EMA

Regional and national HTA bodies provide recommendations on medicines and other health technologies that can be **financed or reimbursed by the healthcare system in a particular Member State or region.**

The assessment criteria used by HTA bodies **differ between Member States,** in accordance with regional and national legislation.

On market = Access to a new medicine at national level

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The main challenges of the strategy

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The main challenges of the strategy

1. **Children are not in the right position** -> paediatric medical therapeutic needs are not the determining factor in R&D strategies of the pharma industry; Lack of proper Incentives & Low profits & Low Priority

2. **Clinical Research work at the hospital (site) level is not sufficiently funded by the available instruments** (not about individual trial funding, but the practical infra between the trials!)*

3. **The unequal access to medicinal products at national level -> not systematically / regularly monitored and analyzed at EU level** (= RW product availability); Pricing principles & Business strategies

   -> *Example; Nordic database review*

*Variation between countries and hospitals

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Example: Latest Nordic database review (submitted 09/2020)

Does the EU's Paediatric Regulation work for new medicines for children in Nordic countries? A retrospective database review.

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Competing Interests
The authors declare no competing interests. P. Lepola is the Chair of the European Network of Paediatric Research at the European Medicines Agency (Enpr-EMA). S. Wang, A. M. Tötterman, N. Gullberg, and K. M. Harboe are members of the Paediatric Committee at the European Medicines Agency. The views and opinions expressed in this article are those of the authors and do not necessarily reflect the policies or positions of the Paediatric Committee or the European Medicines Agency.

Design
This is a retrospective analysis of the national Medicine Agency's databases in Denmark, Finland, Norway and Sweden. Products in the Annex of European Medicines Agency´s (EMA) EU Paediatric Regulation 10-year report; -> whether a product was still authorised and whether the product was marketed at the time of the study period between January and March 2019.

Conclusions
This study reflects the reality of the implementation of the Paediatric Regulation. The results show that several new medicinal products and new formulations targeted at children are not marketed. This directly affects the availability of these medicines. These findings indicate the need to further investigate how to facilitate the availability of new medicines for children across Europe.

Open access
This is an open access article.

Remarks of the results: Despite the intentions of the EU Paediatric Regulation, medicines targeted at children are not all marketed, risking limitations in access and availability.

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Regulatory challenges - I

- **PIPs not addressing the real paediatric medical needs**
- **International collaboration limitations per jurisdiction**
  - Competent Authority requirements
  - Ethics Committee´s requirements
  - CTA requirements
  - Timescale of paediatric R&D plans of the industry
- **HTA process and pricing**
  - Separate from research processes
  - Done at national level
  - Not under EU regulatory remit / influence

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Regulatory challenges - II

- **EU regulatory bodies have limited legislative power** on
  - deciding priorities
  - limiting pharma business on focusing certain development targets
  - regulate pricing
  - Influence on national policies
- **Paediatric research networks and expertise is under utilized**
  - Enpr-EMA networks, learned societies and the various expert´s communities / organizations can provide focused scientific assistance and advice, but these has not been used as much as there is potential available

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Scientific challenges

- **Limited number of patients – small populations (-> global)**
- **Childhood is not strategically the starting point** of the
  - Industry R&D strategies
  - Funding programs (EU / national)
  - Resource support at all levels of operative activities
  - Clinical Trials are not seen as "hard science"
- **Not (yet) enough commonly accepted harmonization**
  - procedures, practices, methodologies, tool, guidelines etc. at EU / global level
- **Not enough professional training programs for clinical staff**
- Rare "niche" area of science – **very few experts**

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Clinical challenges

- Highly human resource intensive (> 60% of the trial budgets)
- Performed in addition to normal clinical work (not highest priority in health care setting)
- Performed usually in publich health care units (i.e. hospitals)
- Competes of time & resources with normal clinical work (when done amongst patients in in-patient settings)
- Not all phycicians / nurses are intrested in research work
- Out-patient settings / preventive health care units (vaccinations and healthy infants etc.) has different priorities (e.g. national vaccination programs)

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Public challenges

- Low awareness about the clinical research and the benefits
- Low P&P involvement rate to R&D processes (design -> conduct)
- Low involvement to ethical "pre-review" processes
- Children´s Rights not fully considered
- Different languages and cultural / religious traditions and requirements – even in EU/EEA area
- Not enough easily accessible info materials in various languages and in various formats (electronic, printed, videos etc.)

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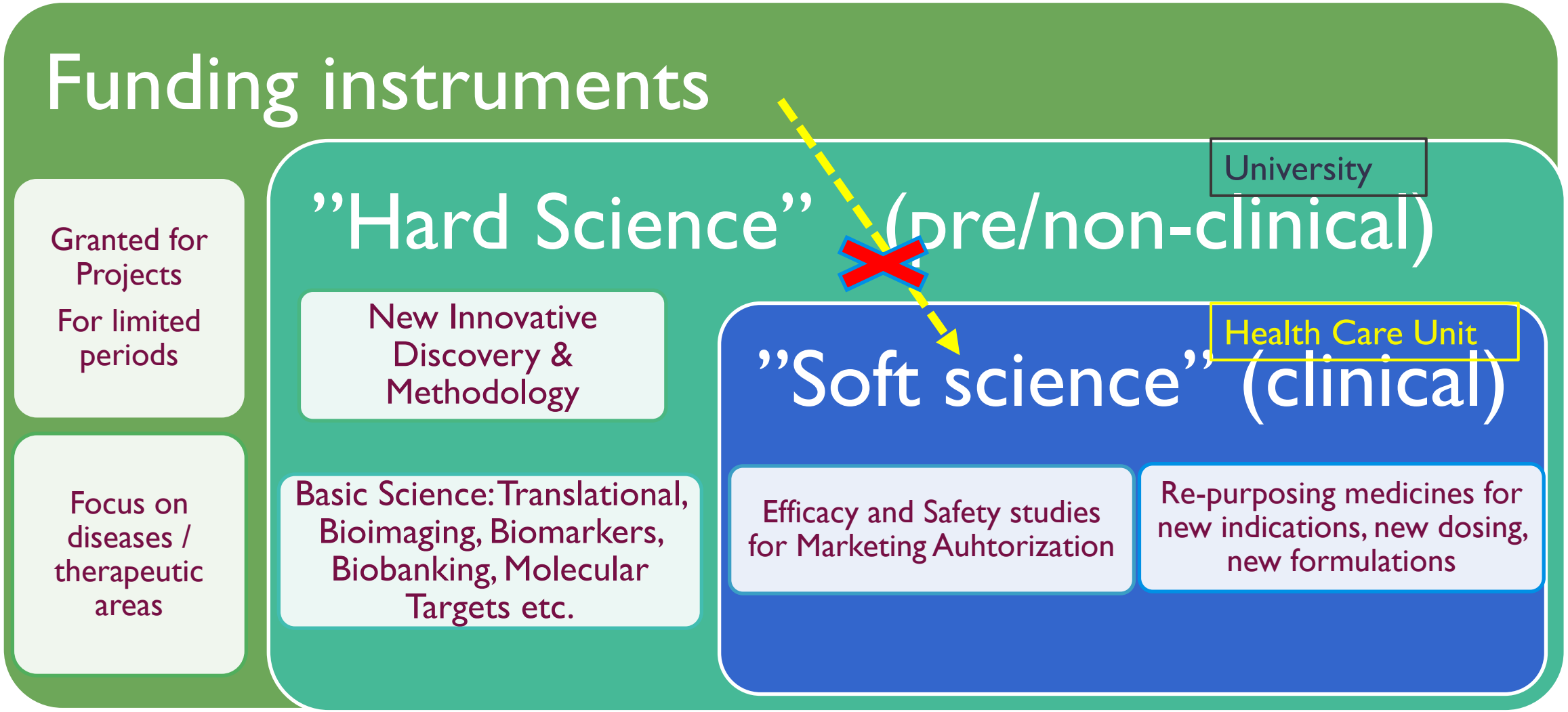
Funding challenges I



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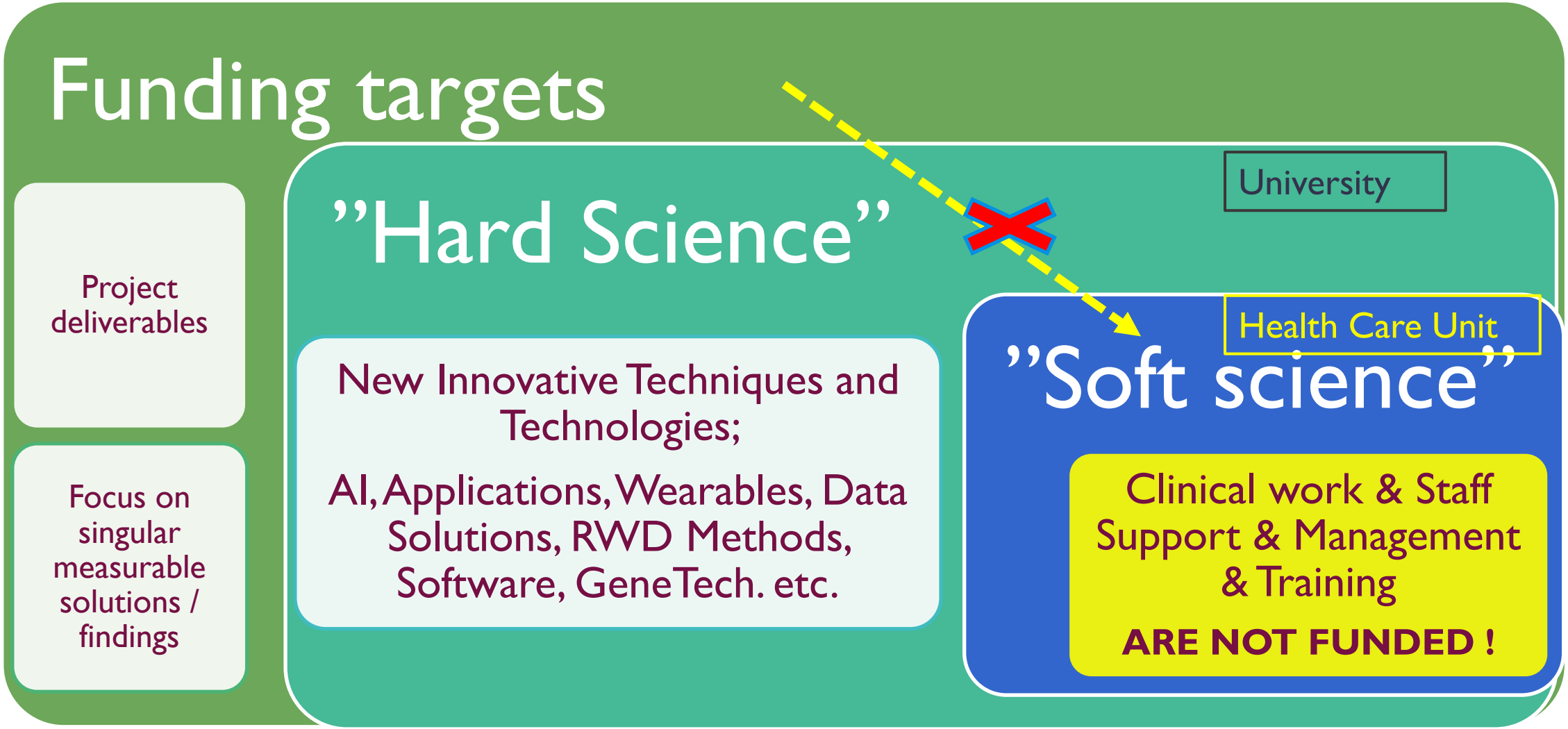
Funding challenges II



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Proposals to consider for the strategy

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Proposals to consider for Strategy I

- A patient-centered forward-looking strategy must ensure that **children are placed into the correct position**
  - Across all age groups and all therapeutic areas
  - Design and development process should include children from the beginning
- **Treatments should be available for children from early state after diagnosis**
  - Rapid access to new medicines will increase QALYs (quality-adjusted life-years) of individuals and saves health costs, which ultimately represents a positive impact on the economy and society - as a whole.

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Proposals to consider for Strategy II

- **Children and adolescents should not simply be categorized as a vulnerable group**
  - There is a clear distinction to be made between legal and ethical vulnerability – and the real medical need (not "over-protecting")
  - Same principle applies to another vulnerable population; pregnant women, for whom normal general adult data cannot be fully extrapolated either
- **Support of the research environment and clinical trial sites via various funding schemes**
  - The development of sustainable national and pan-European clinical research networks and infrastructures will be necessary to ensure delivery of paediatric clinical trials and data of high quality in the most cost-effective manner

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Proposals to consider for Strategy III

- **Paediatric drug development must not be considered as a separate business** but should be integrated with adult drug development from the start and based on paediatric needs.
- **Development (negotiate) of suitable mechanism to correct the economical "business bias"** regarding R&D costs and pricing
- **Development of a method to support collecting and using published academic origin product data**, to extend product development for potential re-labelling and re-purposing for use in children.
- **Development of regular review process of the** (paediatric and orphan) **medicinal products availability**; products having active MAA in EU/EEA, at national level markets and regular analysis on this data.

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Proposals to consider for Strategy IV

- **Enpr-EMA and it´s all member networks can provide targeted assistance on definging and addressing the medical unmet needs of paediatric patient population**
  - Can be done by therapeutic areas if needed
  - Can be done in collaboration with patients & parents groups
  - Have international collaboration access to other regions
  - Have potential to support multistakeholder –meetings

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Summary

- Placing children into the right position with relevant medical / therapeutic needs would enhance the situation
- Supporting research and ”soft science” with new funding instruments and funding schemes would facilitate also clinical research work
- Utilizing more effectively patients, specialized experts and research networks would speed-up the development processes
- Supporting collection and usage of the published academic origin product data for re-labelling and re-purposing existing products would support wider product availability and treatment options
- Developing new EU-level monitoring procedures to evaluate regularly the product availability at national level would support decision making processes
- Increasing more transparent discussions what is fare and acceptable, and by what costs, would enhance mutual understanding, solutions and commonly accepted decisions

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- ***Thank you for your attention!***

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23 October 2020
Virtual meeting

XIII FORESIGHT TRAINING COURSE
Challenges for Researchers and Regulators facing the pandemic crisis

Discussant on "Safe and accessible medicine for children: how to change the Paediatric Regulation"

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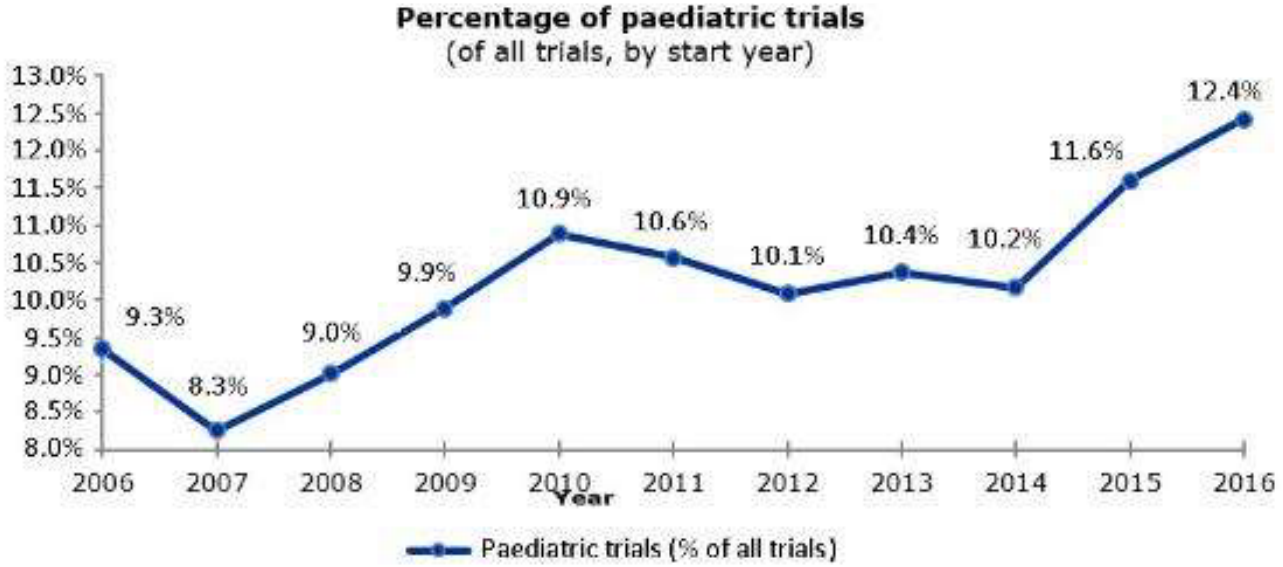
Paediatric Regulation impact

1 The Paediatric Regulation has helped to boost **paediatric clinical research**, to increase availability of products with paediatric indications in the EU market and to improve available information on these medicines

2 The vast majority of stakeholders who responded to a public consultation thought the Paediatric Regulation had a positive impact



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Paediatric Regulation's revision insight

Why a revision is to be addressed
In its 2016 Resolution, Parliament recognised that the Paediatric Regulation has been beneficial to children overall, but **less effective in certain therapeutic areas** (e.g. paediatric oncology and neonatology). It therefore called on the Commission to consider revising the Regulation.
The ten-year report on the implementation of the Regulation, revealed specific challenges: 1- developing medicines for **diseases that only affect children** or that manifest differently in adults and children. 2- **availability is delayed** when compared with adult medicines.
EC/EMA Action Plan on Paediatrics 2018

Topic areas
• Identifying paediatric medical needs
• Strengthening of cooperation of decision makers
• Ensuring timely completion of paediatric investigation plans (PIPs)
• Improving the handling of PIP applications
• Increasing transparency around paediatric medicines

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Paediatric Regulation's revision insight

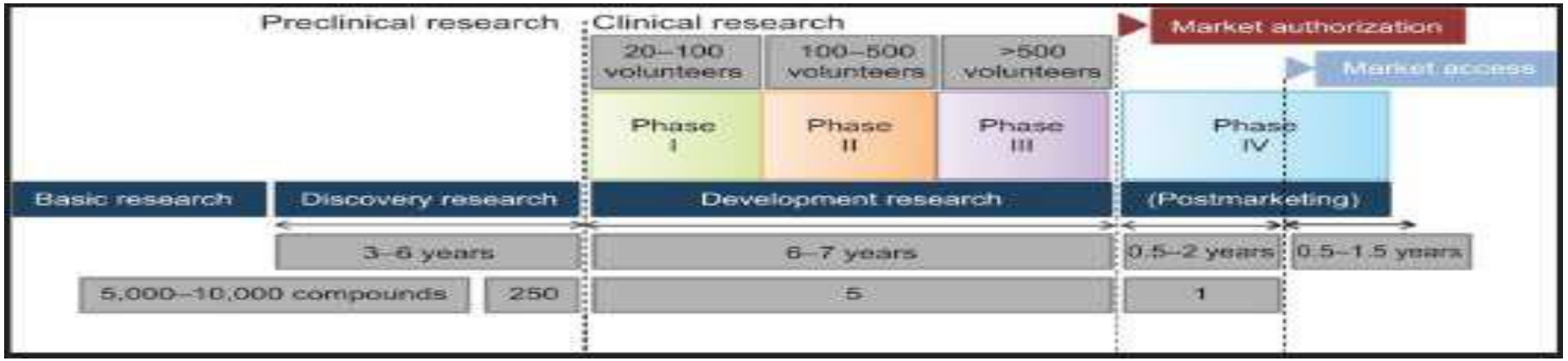
Why a revision is to be addressed

The Pharmaceutical Strategy document, anticipate the will to revise the Paediatric Regulation but is not including any practical alternative

The COMMISSION STAFF WORKING DOCUMENT JOINT EVALUATION mention as points of interest for implementation

major therapeutic advances have mostly failed to materialise for diseases that are rare and/or unique to children

The Regulation has no effective instruments for channeling R&D into specific therapeutic areas



Drug development is complex: specific references to the development need of paeditric (and orhan) are needed

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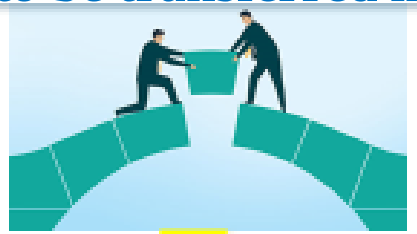
Paediatric Research integrated approach

One suggestion is to adress paediatric research trough an integrated approach in term of target, mechanism of action, genetic biomarkers, developmental pharmacology, paediatric data storage and exchange to be transferred into the paediatric clinical phase



EPTRI contribution

To aggregate a large research community focused on **preclinical and translational research for** paediatric medicines

To promote an **integrated approach to paediatric drug development** by contributing to clinical studies implementation

To implement in the paediatric medicines discovery and development fields, **innovative methods and technologies currently not available or underused**

New target for paediatric/rare disease
Pre-clinical package
MoA and effect size
Developmental Pharmac/phase 0 study
Paediatric Biomarkers
Formulation .....

ePTRI
European Paediatric Translational Research Infrastructure

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Question

- Which is your feeling on this integrated approach?
- Which contribution from EPTRI to the clinical paediatric research sector could be foreseen?
- Which new instruments can foster innovation for the development of medicines for small populations?
- Which rules can force pharma companies not only to submit a PIP but also to timely develop the paediatric drug and to negotiate a joint pricing together with the adult drug?

❖ Which influence patenting systems can have on research and development on new and innovative medicines in the area of diseases where there is no profitable market?

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Orphan and paediatric medicines share similar features

But…in the paediatric population a double gap exists

60-80% of Rare diseases affect children:

- Many rare diseases are genetic
- Start early in life
- Affect growth, sexual and CNS maturation during the developmental process

Few specific information available because:

- Small number of patients affected by each condition
- Few resources invested
- Use of medicines not specifically tested (off-label, unlicensed)
- Few evidence available from published non registrative studies

Children are 'orphan' 2 times…

…2 Regulations available

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The TWO REGULATIONS are different

Regulations Background is similar
Public research funding was often the only means available to support neglected fields
Both the areas of rare diseases and medicines for children are characterized by market failure and need incentive to the market

Orphan Regulation

The purpose of the Orphan Regulation is to reward R&D through incentives and, ultimately, to place medicines for RDs on the market, where there was previously no commercial interest.

Paediatric Regulation

The Paediatric Regulation, works with obligations. It compels companies for testing the possible use of their medicines in children and only provides rewards once this obligation has been fulfilled,.

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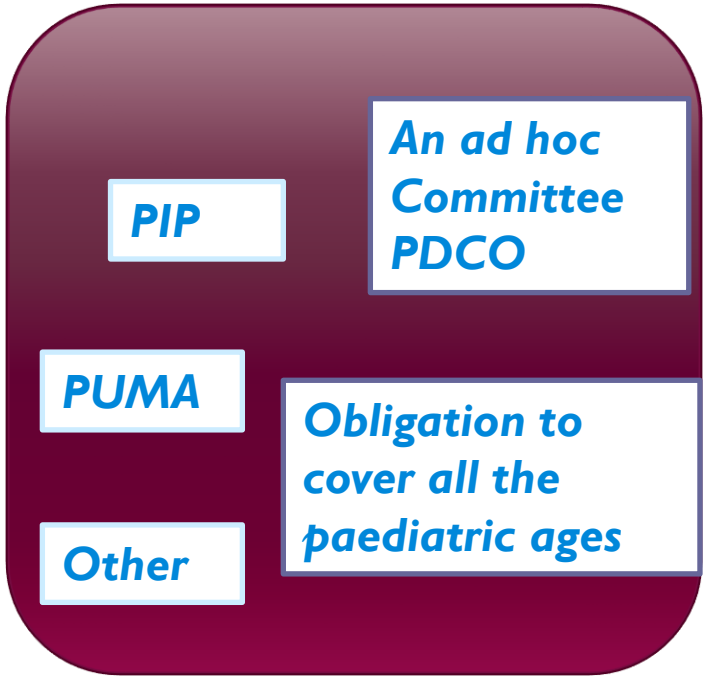
Questions

Which risk we should avoid by dealing with the proposal of revision?

Which requirements specific of the Paediatric Regulation you consider not negotiable ?



Which requirements specific of the Orphan Regulation would you like to translate in the paediatric legislation?