EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

The Value of a Neonatal Consortium: A Regulator's Perspective

Applying Regulatory Science to Neonates:
Launch of the International Neonatal Consortium

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Presented by Ralph Bax on 17 May 2015
Paediatric Medicines, Product Development Scientific Support Department

Disclaimer

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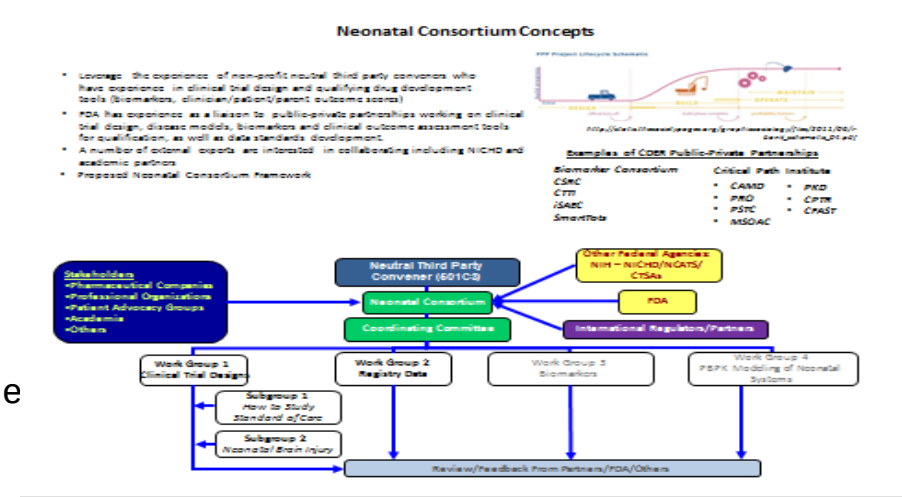
Value of a Neonatal Consortium – first thoughts

- First steps
  - **Concepts**
  - Oct 2014: 1st annual workshop
    Roadmap for Applying Regulatory Science to Neonates (C-Path/FDA, Silver Springs)
  - March 2015 Collaboration between Researche medicines for neonates
- Complexity - Collective Intelligence
- Competition – Co-operation → "Co-opetition"?
- → Consortium



Preterm birth rates

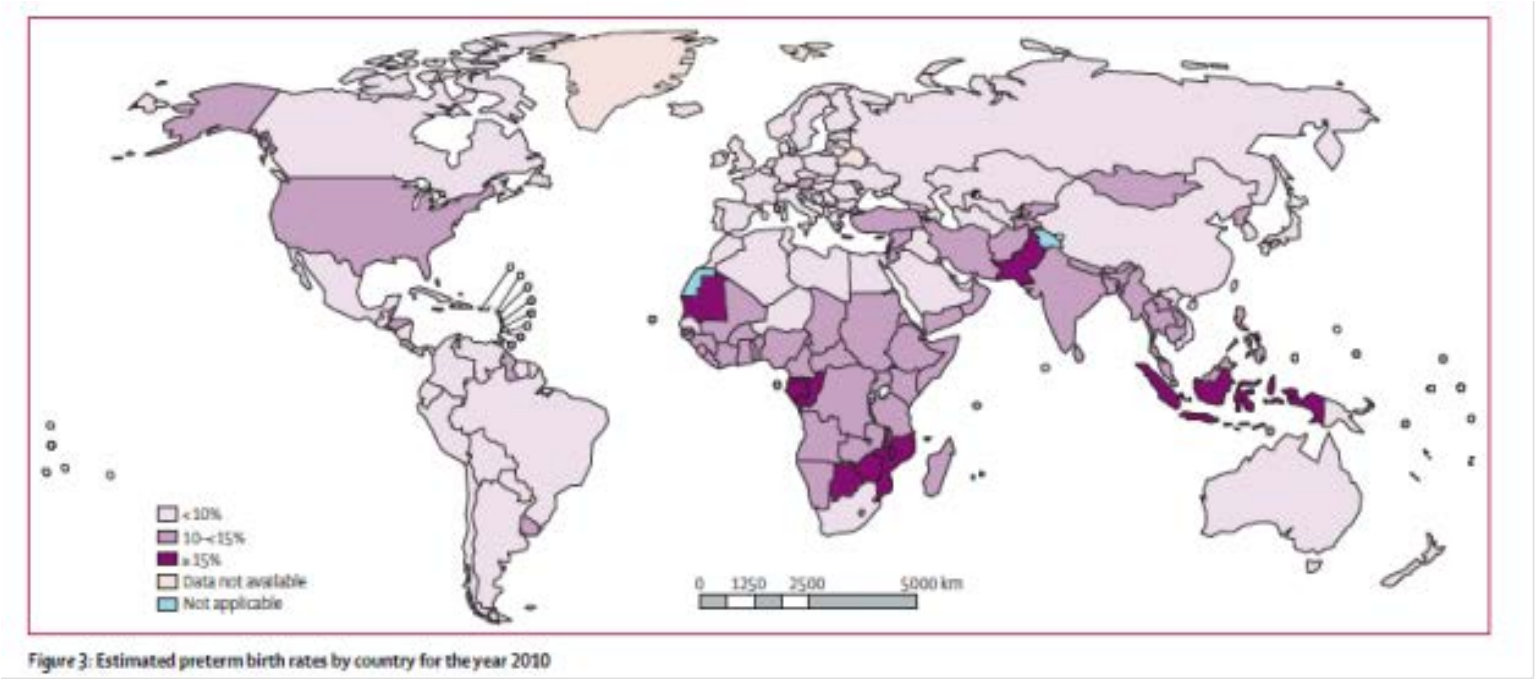
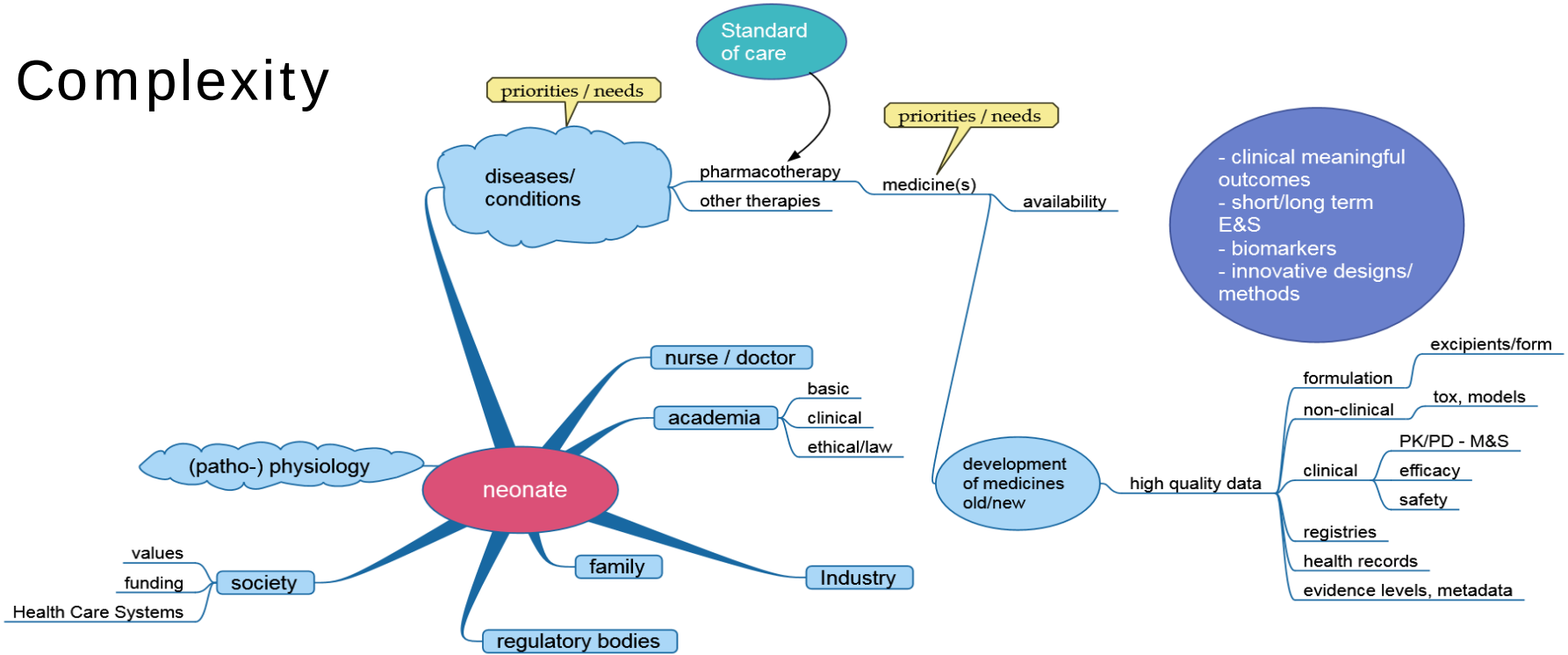


Figure 3: Estimated preterm birth rates by country for the year 2010

Blencowe H et al, Lancet 379: 2162–72, 2012

Complexity


Standard of care
priorities / needs
diseases/ conditions
pharmacotherapy
other therapies
priorities / needs
medicine(s)
availability
- clinical meaningful outcomes
- short/long term E&S
- biomarkers
- innovative designs/ methods
nurse / doctor
academia
basic
clinical
ethical/law
(patho-) physiology
neonate
development of medicines old/new
high quality data
excipients/form
formulation
non-clinical
tox, models
PK/PD - M&S
clinical
efficacy
safety
registries
health records
evidence levels, metadata
values
funding
Health Care Systems
society
family
Industry
regulatory bodies

EU Legislation - reminder

- **PIP** (Paediatric Investigation Plan) needed for the initial authorisation of new products (and variations for on-patent products) -including only-adults indications- in the EU.

- Studies in neonates and children need not necessarily be done at the same time as in adults (**deferrals** > 80% of cases).

- Reasons to **waive** studies in children:
  - Likely to be ineffective or unsafe
  - Condition does not occur
  - No significant therapeutic benefit over existing treatments

Neonates in Paediatric Investigation Plans

- 1 in 4 PIPs specifically mention neonatal development
- Inclusion of neonates increased in PIPs: from 15% to 28% (2008) and from 24% to 32% (2011).
- Further outcome analyses ongoing/planned
  - Therapeutic areas
  - Non-clinical studies
  - Global Research in Paediatrics (GRIP, FP7) network: How to arrive at the first dose for neonates.

Paediatric Investigation Plans agreed in prioritised areas

Age group	Brain	Lung	NEC	Sepsis	ROP	NAS
Neo only	Perinatal Asphyxia - 2-iminobiotin	Prevention of BPD - budenoside - azithromucin	./.	Prevention - pagibaximab	Treatment -ranibizumab	./.
Neo incl	AED/Neonatal seizures - retigabine - lacosamide - carisbamate - brivaracetam	PAH/PPHN - treprostinil - sildenafil - tadalafil - riociguat - bosentan - macitentan		Treatment - vancomycin - meropenem - eritoran - trombomodulin alfa - ceftriaxone / sulbactam		
				- isavuconazonium - pozaconazole - caspofungin		

NEC necrotising Enterocolitis
ROP retinopathy of Prematurity
AED antiepileptic drugs
PAH Pulmonary arterial Hypertension
PPHN Pulmonary Hyper-Tension of the Newborn
NAS Neonatal Abstinence Syndrome

Paediatric Investigation Plans agreed in other areas

Age group	Pain	Cardiovascular	Nutrition
Neo only	- paracetamol (moderate, fever, iv)	Treatment of neonatal circulatory failure: - dobutamine	Prevention of growth retardation due to lack of bile-stimulated lipase in enteral nutrition: -bucelipase alfa
Neo incl	- glucose (procedural) - tapentadol (acute/chron) - morphine (moderate severe/prolonged) - fentanyl citrate (acute, pre-medication)	Treatment of hypotension in the extremely low gestational age newborn. - dopamine	Supplementation of amino-acids where parenteral nutrition is required. - Neoven

Value of an INC - regulator's point of view

- Public Health Need– more and better, safe and effective medicines for neonates
  - Increase high quality, ethical **research** into medicines for children
  - Increase **availability** of authorised medicines for children
  - Increase **information** on medicines
  - Without unnecessary studies in children/delaying authorisation for adults
- EnprEMA, Support funding initiatives, Paediatric Inventory
- INC
  - Additional platform/channel for communication and proactive work
  - Most efficient use of regulatory tools (e.g. PIP, SA, qualification of novel methodologies)
  - Learning from other stakeholders

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Thank you for your attention

Further information

paediatrics@ema.europa.eu

European Medicines Agency
30 Churchill Place • Canary Wharf • London E14 5EU • United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

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EnprEMA

- **Enpr-EMA = European Network of Paediatric Research at the European Medicines Agency**

  http://www.ema.europa.eu/ema/index.jsp?curl=pages/partners_and_networks/general/general_content_000303.jsp&mid=WC0b01ac05801df74a

- **Enpr-EMA is a network of research networks, investigators and centres with expertise in performing clinical studies in the paediatric population with the mission of facilitating drug trials in order to increase the availability of medicinal products authorised for use in the paediatric population .**
- **Working group 4: Dialogue and Interaction with Ethic Committees**

Breakdown of networks by type and category

National	Oncology / Haematologic Malignancies	Diabetes / Endocrinology / metabolic disorders / Gynaecology	Gastroenterology / Hepatology	Allergology / Immunology / Rheumatology	Stem Cell / Organ Transplantation / Haematology / Haemostaseology	Respiratory diseases / Cystic Fibrosis
NIHR-MCRN	Newclastle-CLLG		ESPGHAN	PRINTO	EBMT	ECFS-CTN
ScotCRN	EPOC		PEDDCReN			
FinPedMed	ITCC			JSWG of PRES	IPTA	
MCRN-NL	IBFMSG					
MICYRN	CLG- of EORTC					
CICPed						
IPCRN						
NCCHD						
BLF						
RIPPS						
Futurenest CR						
SwissPedNet						
Red SAMID						
NCCHD-Japan						

Category 1: Networks fulfilling all minimum criteria.
Category 2: Networks potentially fulfilling all minimum criteria – but needing to clarify some issues.
Category 3: Networks currently not yet fulfilling minimum criteria.
Category 4: Networks not performing clinical trials; e.g. methodology, infrastructure, etc.

Unable to fill self-assessment

SPECIAL ACTIVITIES / AGE GROUPS

Cardiovascular diseases / Nephrology	Psychiatry / Neurology	Infectious diseases / Vaccinology	Intensive Care / Pain / Anaesthesiology / Surgery	European neonatal network	European paediatric pharmacists	special activities (Phv, long term follow up, community paediatricians)	Expertise in clinical trial methodology
	EUNETHYDIS	PENTA-ID	Pediatric Critical Care	GNN		FIMP-MCRN	TEDDY
		UKPVG		EuroNeoNet			PRIOMEDCHILD
				Neo-circulation			ECRIN
				INN			GRIP
				ESDPPP			

Need for clinical trials in neonates

Vulnerable population, often treated with multiple medicines at the same time (up to 60)

Just like children are not small adults, neonates are not small children, therefore extrapolation of efficacy or safety from older children is very often inappropriate

Neonates are the paediatric population for which less data are available on the correct use of medicines

Gradual maturation of metabolic and detoxifying pathways during the first months of life cause different sensitivity and response to active substances and excipients

Ethical and scientific arguments in favour of protecting children through clinical trials, not from them

Higher incidence and severity of adverse drug reactions in “off-label” use of medicinal products

Efficacy cannot be assumed when prescribing medicines not tested in the appropriate population

Inclusion of a child in a clinical trial is likely to be associated with a better outcome than “off-label” use

Failure to conduct clinical trials in children is unethical as it forces physicians to do uncontrolled experiments almost every time they prescribe a medicine to a child