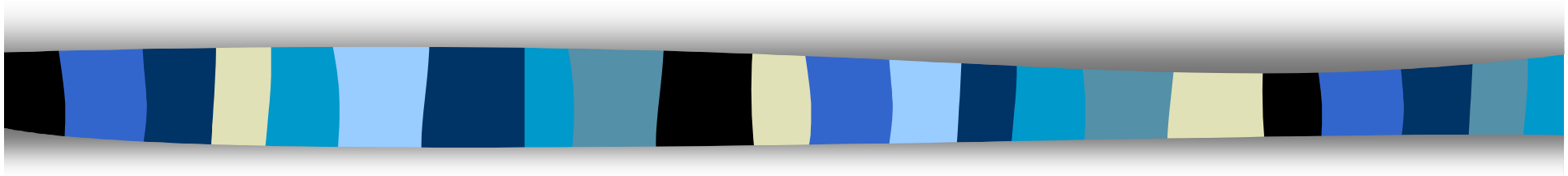
Achievements and outstanding challenges in medicines for children



José Ramet MD PhD

CESP

Why bother about children?

CHILDREN ARE DIFFERENT

THEY CANNOT TAKE THEIR MEDICATIONS LIKE ADULTS

- 1/ cannot swallow tablets or capsules < 6 y.
  ➔ need specific drug formulations:
  solutions, suspensions, drops, powder, microgranules

2/ formulations with good acceptability

3/ iv formulations: appropriate concentrations

Why bother about children?

CHILDREN ARE DIFFERENT

DRUGS « BEHAVE » DIFFERENTLY IN CHILDREN

the fate and the effect of drugs : different

- the magnitude of the response
- the nature of the response
- some side effects: only in children
- growth and maturation

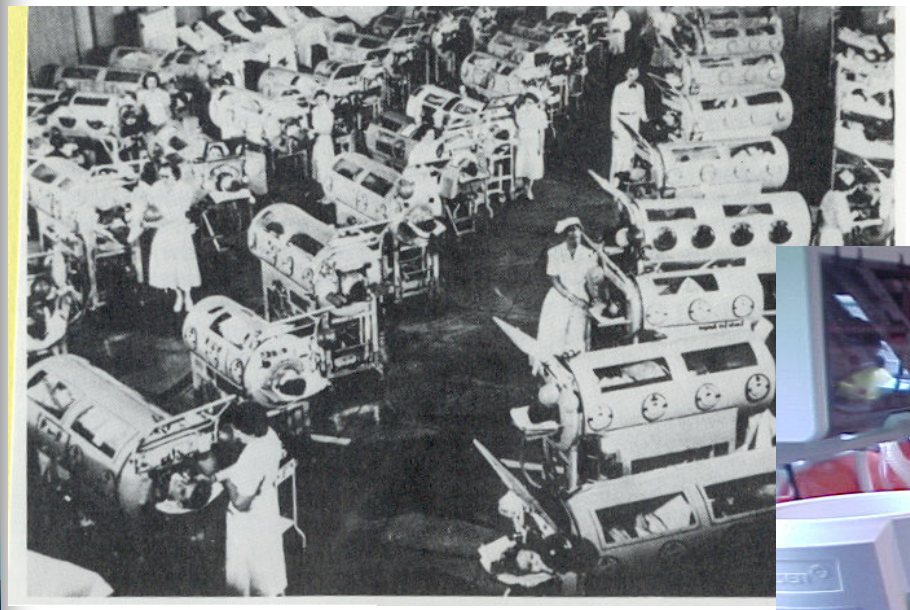
Why bother?

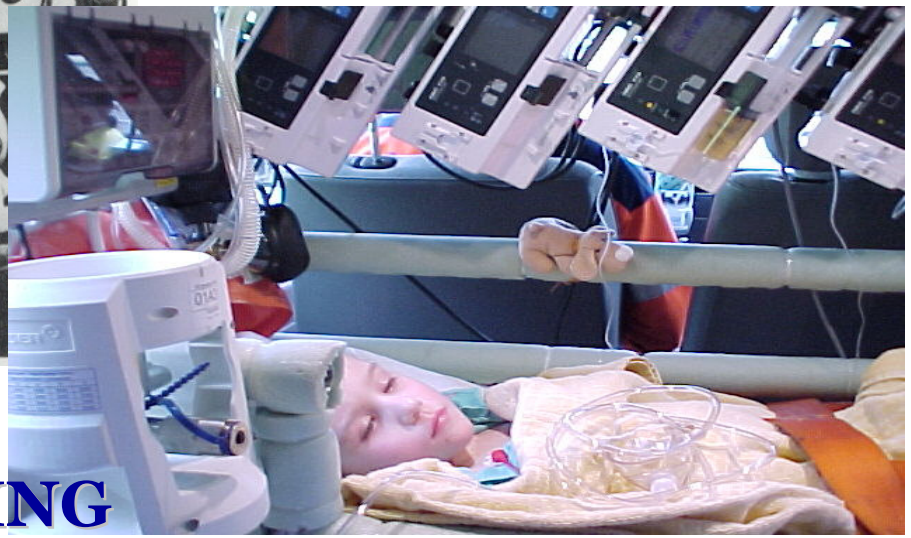
Exploring specific needs for paediatrics?

- **Paediatrics in the European Union**
  - 0-16 years : about 20% of total population
- **Needs:** 0-16 years group : specific sub-populations
  - neonates to teenagers
  - different developmental and behavioural characteristics
- **Specific:** :Estimation: over 50 % of medicinal products used in children :

  never been specifically evaluated for use in children

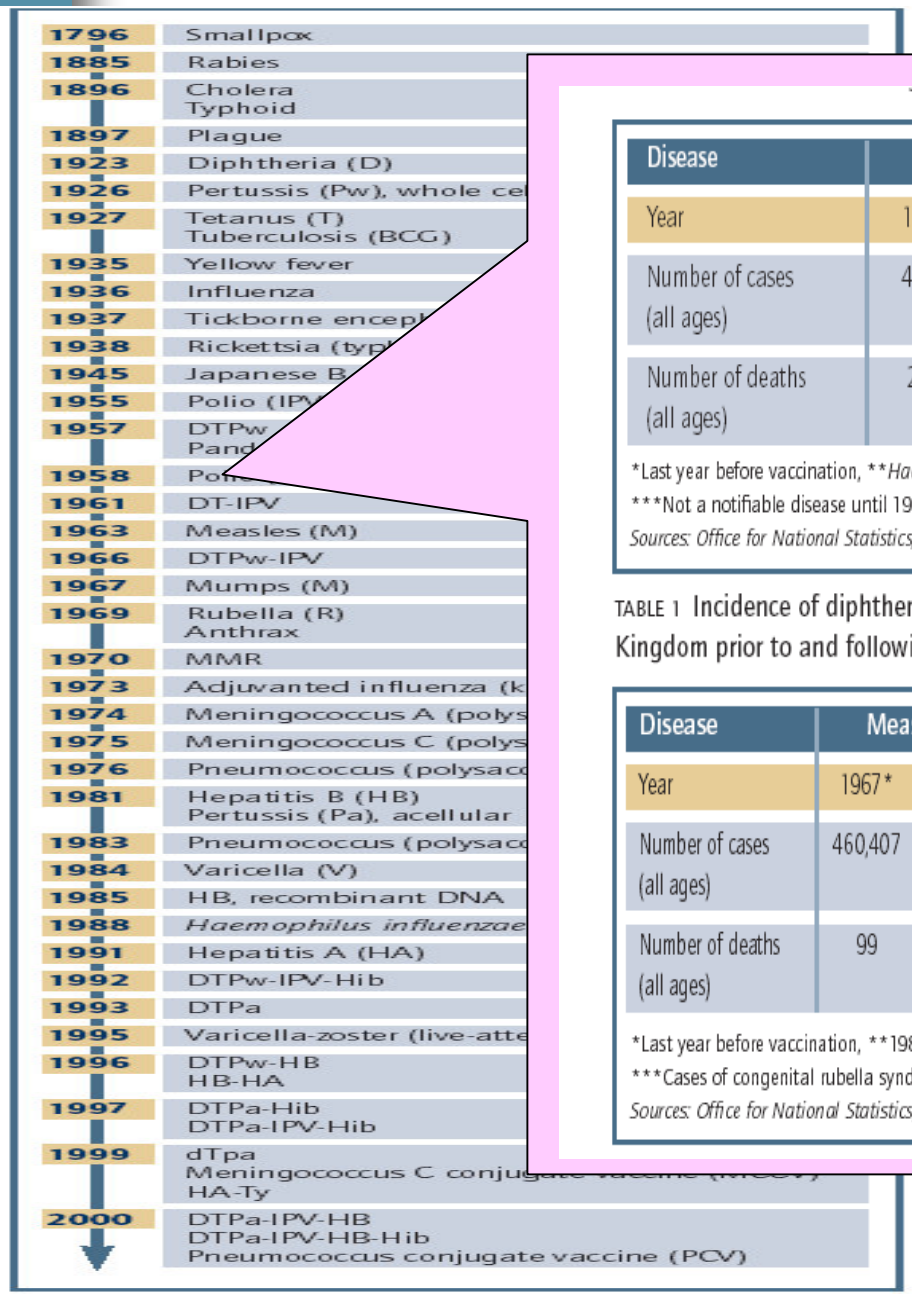
- 50 years
- Major evolution





KNOWLEDGE, TRAINING

TECHNIQUES and RESEARCH



Disease	Diphtheria		Tetanus		Pertussis		Hib meningitis**	
Year	1939*	1996	1960*	1996	1956*	1996	1991*	1996
Number of cases (all ages)	47,061	12	NA***	8	94,410	2,387	417	38
Number of deaths (all ages)	2,133	0	32	0	92	2	22	0

*Last year before vaccination, **_Haemophilus influenzae_ type b meningitis,
***Not a notifiable disease until 1968
Sources: Office for National Statistics, Public Health Laboratory Service

TABLE 1 Incidence of diphtheria, tetanus, pertussis (whooping cough), and Hib meningitis in the United Kingdom prior to and following the introduction of vaccination

Disease	Measles		Mumps**		Rubella**		CRS***		TB	
Year	1967*	1996	1989*	1996	1989*	1996	1971*	1996	1952*	1996
Number of cases (all ages)	460,407	5,613	20,713	1,924	14,750	9,081	162	21	48,093	5,859
Number of deaths (all ages)	99	0		0		2			10,590	420

*Last year before vaccination, **1989 was the first full year of notification for mumps and rubella,
***Cases of congenital rubella syndrome and terminations related to rubella infection
Sources: Office for National Statistics, Public Health Laboratory Service

- **Studies in adults not sufficient**
  - Specificity disease
  - Kinetic characteristics
  - Effects on growth, development, maturation
  - Specific adverse reactions

Child... Not a small adult

Infant... Not a small child

Preterm... Not a small infant

Why conduct paediatric studies?

To meet the medical needs of children

- same rights as adults to receive medicines
- have been shown to be safe and effective

To provide the needed safety /dosing recommendations

To comply with regulatory and legal requirements

Barriers to Paediatric Medicine Development

- Ethical issues
- Off-label prescribing practice
- Investment
- Clinical doability

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Ethical issues

- The paediatric population should :
  - not be exposed to unnecessary hazards
  - not be tested too early in drug development
  - not be tested unnecessarily in clinical trials

- However, the consequence often is that paediatric population :
  - do not receive improved/new medicines : have not been tested
  - they receive off-label medicinal products
    - may get a wrong dose
    - no adequate galenical form
    - no data on safety :

      “since adverse events of off-label use are rarely reported”

Ethical issues

Issues: Ethics committees

- Ethics committees differ significantly in evaluating what is ethical or not
  - Studies in children may involve placebo
  - Sub-therapeutic doses may be used during PK dosing studies
  - Invasive procedures
  - Changes in consent forms
  - …

Barriers to Paediatric Medicine Development

- Ethical issues
- Off-label prescribing practice
- Investment
- Clinical doability

Off-label prescribing practice

A major issue

- when clinical study involves the same medicine being widely used off-label

Makes patient recruitment difficult

Barriers to Paediatric Medicine Development

- Ethical issues
- Off label prescribing practice
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- Clinical doability

Paediatric Medicine Development

Investment- reality

- **The paediatric market is small compared to adults**
- **Paediatric studies are costly**

Additional pre-clinical studies:

Safety eg. juvenile animals, effects on growth & development, long term exposure

Pharmacokinetics eg. children metabolise drugs differently

Development of new formulation:

1. Taste challenges – global variation
2. Allergies, alcohol content
3. Stability, frequency

Paediatric Medicine Development

Robust Clinical Study Design

The most difficult part

- statistical power
- study procedures : minimal

Recruitment

- Adequately cover age groups :neonates to adolescents

Monitoring

- Capturing all adverse events during the study
- Additional monitoring of growth and development
- Long term therapy for chronic diseases

Barriers to Paediatric Medicine Development

- Ethical issues
- Off label prescribing practice
- Investment
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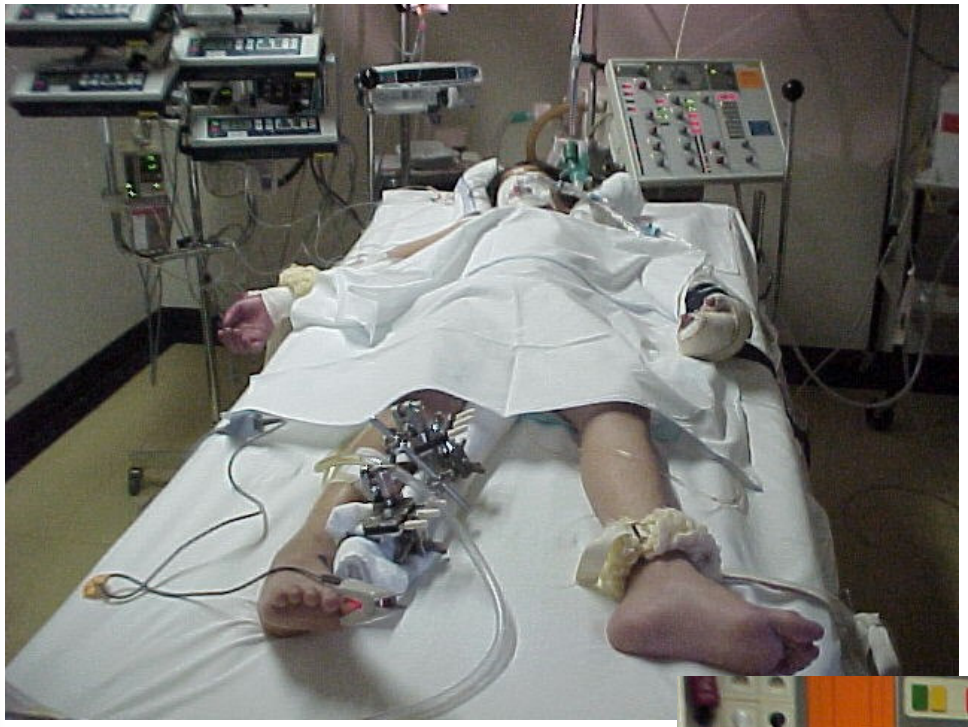
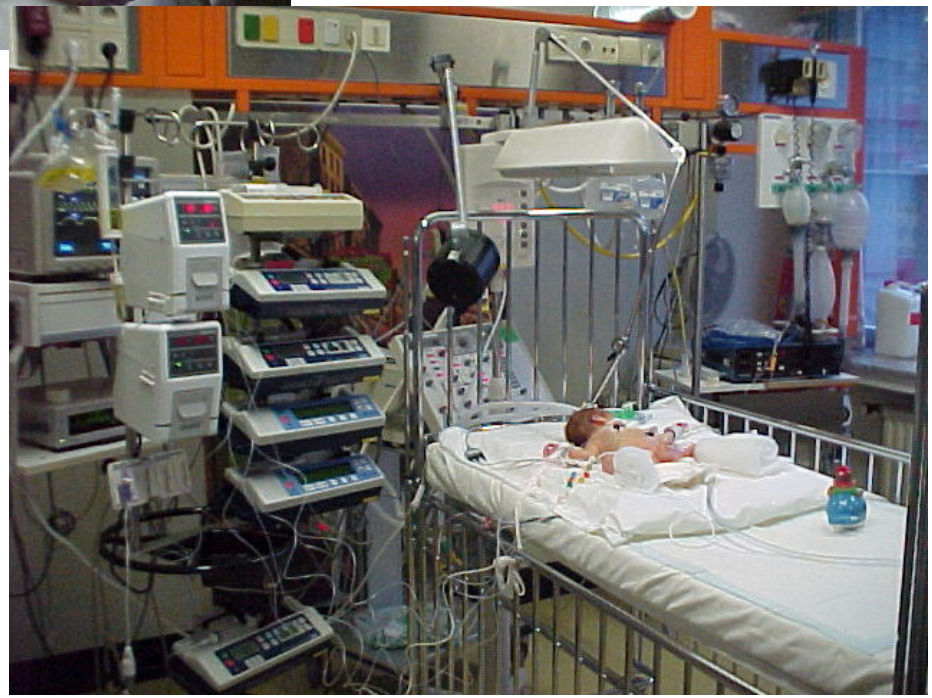
Issues: Clinical Doability

- Generally difficult and therefore lengthy in nature
- Patient population must be representative and realistic – often results in disappointment and de-motivation
- Inadequate facilities at research centre

Achievements in Paediatrics re.to medicines

- **haematology, oncology**
- **organ transplantation**
- **vaccination**
- **asthma**
- **infectious diseases (including HIV)**
- **neonatal respiratory distress**
- **diabetes**
- **psychiatric disorders**
- **cystic fibrosis**
- **pain**
- **…**





Analgesia

Sedation

Antibiotics

Paralyzing drugs

Gastric protection

...

Clinical trials in children : complicated

- historically low : Industry priority list
- due to
  - lack of legislation
  - financial incentives
  - fear to harm children / resulting

caution :paediatric trials
costly in time and money
may need new formulation
ethical challenges
lacking legislation for paediatric clinical trial
smaller market
already using drugs in children on an unlicensed basis

It Takes at Least…..
6 Partners

- Children / parents
- Paediatricians and allied physicians
- Academia
- Industry
- Regulatory Agencies
- Societies

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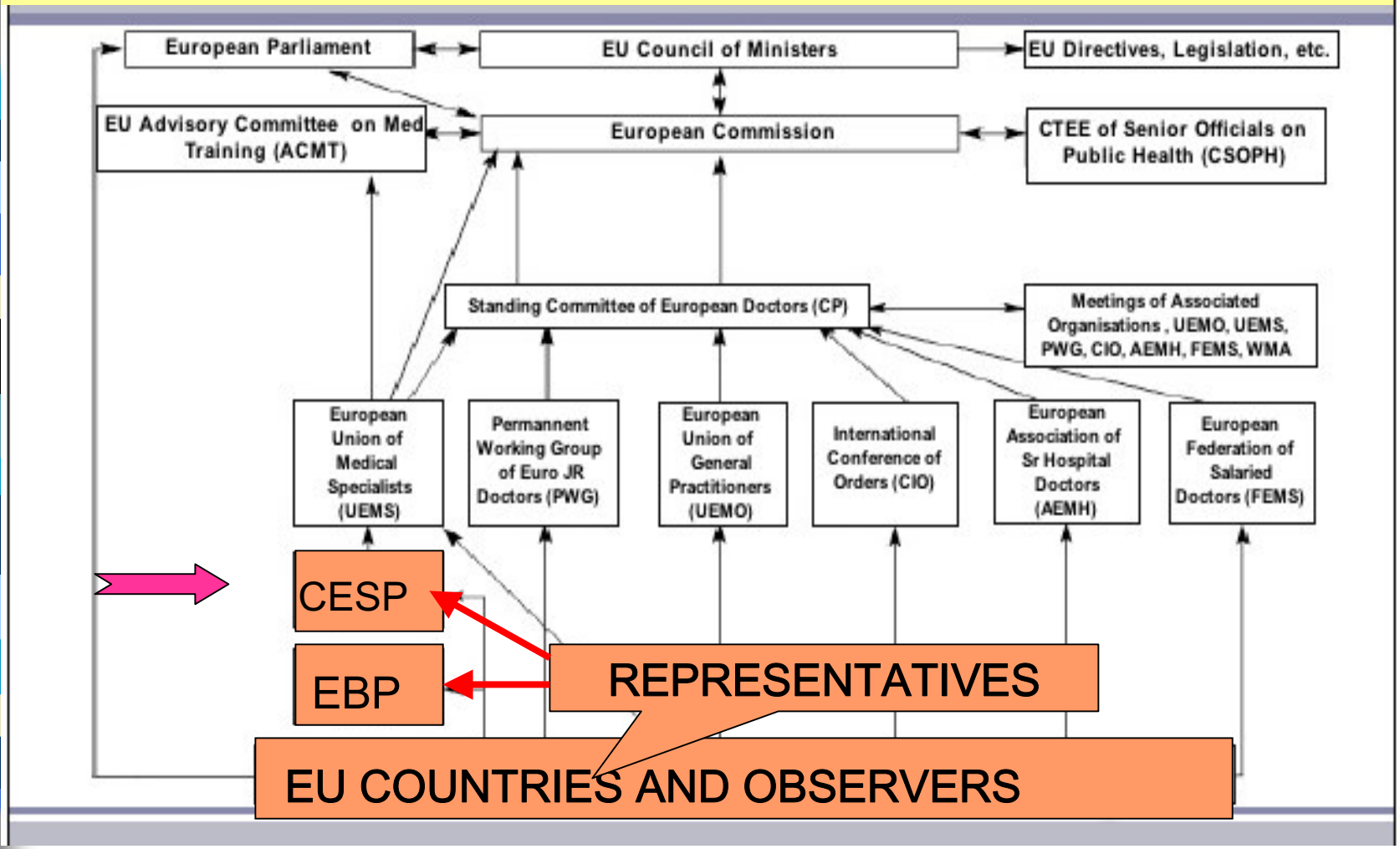
EU Network?

Paediatricians?



"INCENTIVES AND SUPPORT"

Two pleas

First: immediate action for the EC proposal, as time is of the essence.

Second: to keep a very careful watchful eye on the goal of this legislation, which is to foster paediatric research and enhance medicines available for children.

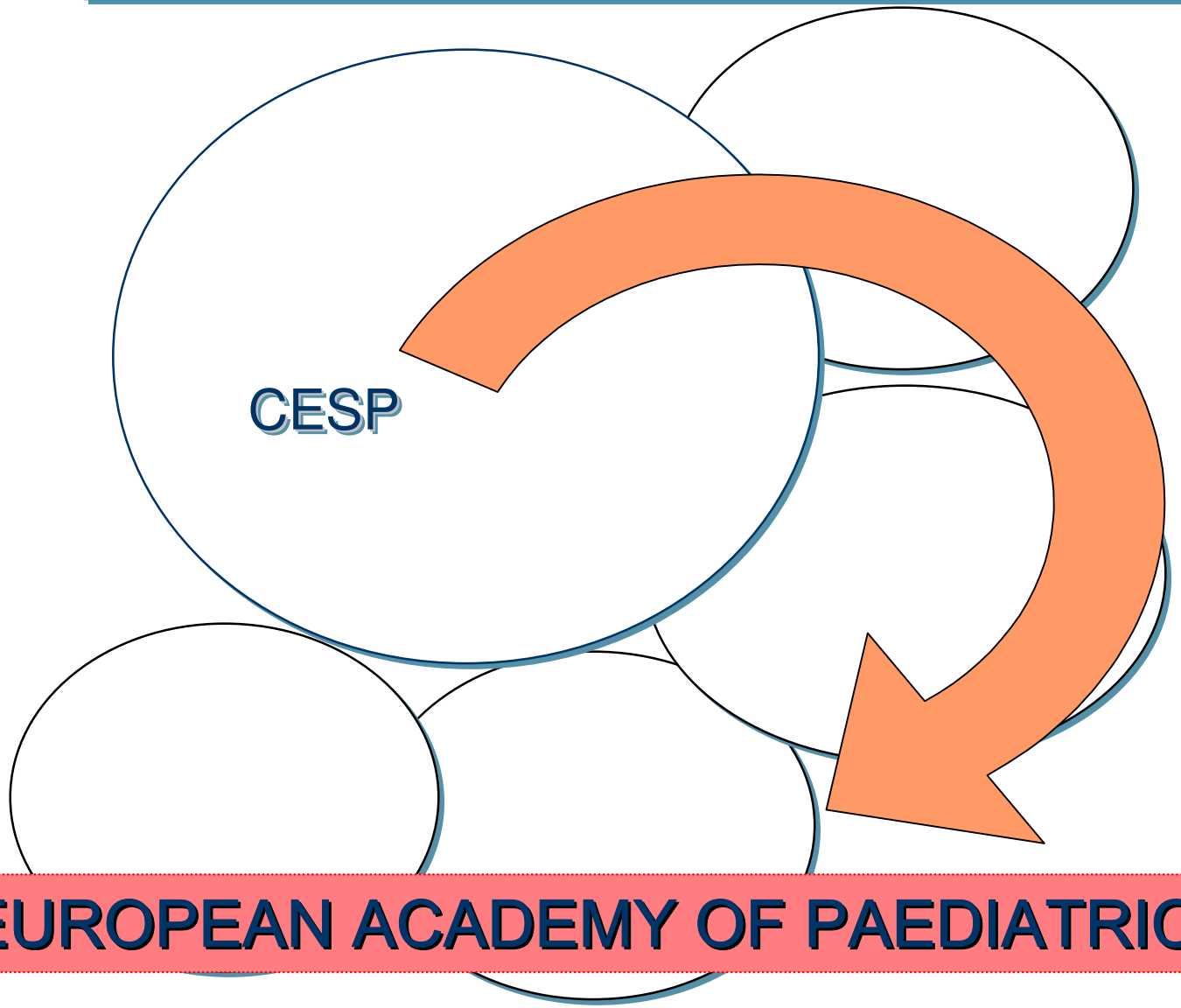
U.S.: the 6-month patent extension awarded to companies completing agreed paediatric research has proven powerful and sufficient

Would this be adequate for Europe?

In this instance, the patent extension must be long enough to

- offset the differences between Europe and the United States

CESP = PAEDIATRIC FEDERATION ?



EUROPEAN ACADEMY OF PAEDIATRICS

It Takes at Least…..
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"It is difficult to make predictions

... especially about the future"

Y. Berra

"INCENTIVES AND SUPPORT"

What should the incentive be?

U.S.: the 6-month patent extension awarded to companies completing agreed paediatric research has proven powerful and sufficient.

Would this be adequate for Europe?

In this instance, the patent extension must be long enough to

- offset the differences be Europe and the United States
- the European medici
- Europe has almost a
- Europe has relatively

Adequate solution?

- incentive : >6 months in Europe?

initiatives on paediatric medicinal products?

- **1. Increase the availability** medicinal products
  suitably adapted to the needs of children by encouraging :
  - appropriate pediatric studies on new medicinal products
  - studies on existing products
  - development of suitably adapted formulations

- **2. Ensuring that pharmacovigilance mechanisms are adapted**
  - Possible long-term effects in specific cases

- **3. Avoiding unnecessary studies**
  - Publication of details of clinical trials already initiated
- **4. List of priorities for research**
  - on existing medicinal products
  - in accordance with health needs
  - priorities in different therapeutic classes

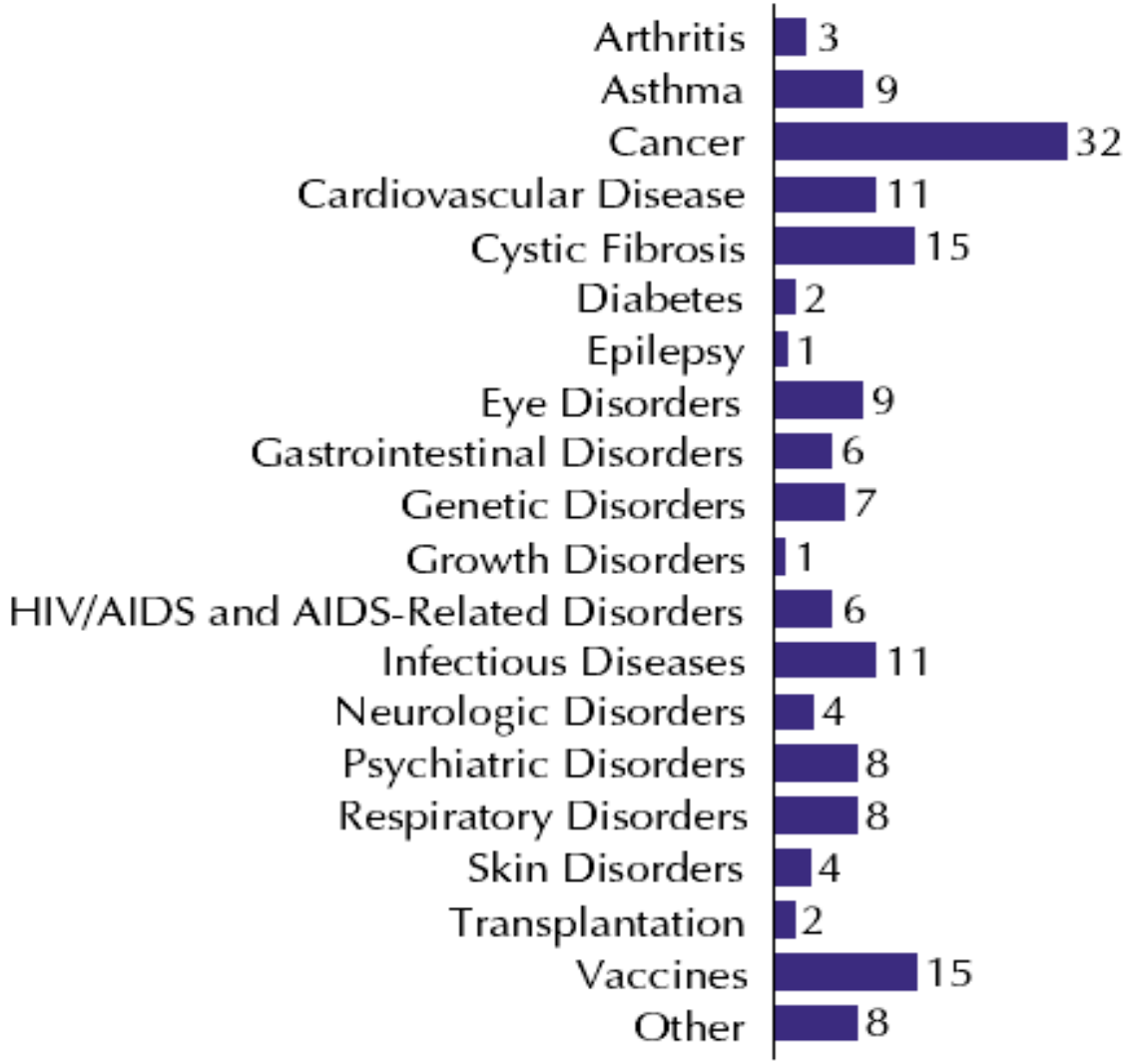
- **5. Expert group**
  - in the field of research
  - development and assessment of clinical trials

- **6. Highest ethical criteria**

Why Partnerships in clinical research in Paediatrics

- Access to and availability of therapeutic advances
  - to all children
- Limit on patient numbers
  - “disease density”
  - Most recent pediatric drug development has been accomplished by international cooperation
- Limit on pediatric investigative expertise
- International regulatory authority
  - acceptance of data
  - avoid unnecessary, duplicative studies

Medicines in Development for Children*



*Some medicines are listed in more than one category.

Why Partnerships in clinical research in Paediatrics

Academic Roles

- Define therapeutics needs
- Develop validated end-points for efficacy and safety, including for PK/PD assessment and "bridges" with adult studies
- Develop effective, efficient, ethically driven networks to conduct clinical studies

Industry Roles

- Discovery of new medicines
  - High throughput screening of compounds
- Development of new medicines
  - Pre-clinical toxicology
  - Human evaluation of dose, safety, efficacy

Dilemmas in Paediatric Clinical Research

- **Dilemma of Health Authorities:**
  - **In the past : protecting children from clinical research**
  - **Now : focused on protecting children by clinical research**
- **Dilemma of Medical Professions:**
  - **Struggling with optimal drug treatment**
  - **Acknowledging ‘over-the-thumb‘ treatments =uncontrolled trials**
- **Dilemma with the Public:**
  - **Children included in trials: science is blamed :**
  - **Children not included : blamed as heartless :**

“use them as guinea pigs"