EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Standards for approval of paediatric medicines

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Is there any benefit from regulatory approval of medicines?

Off label use is widespread in EU

Prescriptions should be based on evidence (benefit-risk)?

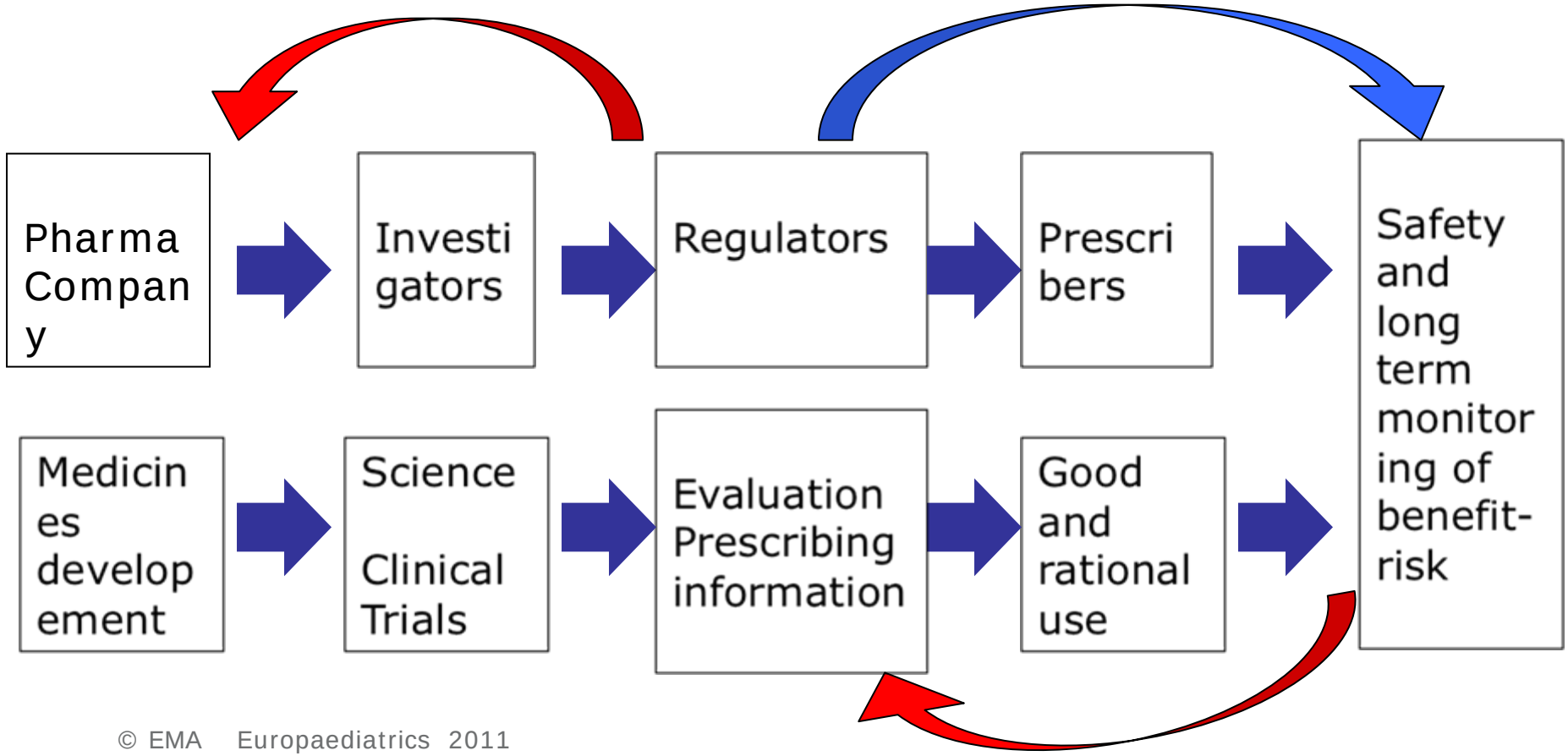
No proper data on dose and safety (and efficacy)

Negative trials are not published and safety data not reported (bias in favour of efficacy)

No approval means no age-appropriate formulation/pharmaceutical form

No approval means no marketing in many countries (and now no reimbursement in some)

A chain of events and responsibilities



What are the standards for medicines?

For children as for adults:

- Efficacy (2 or 1 placebo or active controlled trial(s))
- Safety (non-clinical and clinical)
- 'Quality' (manufacturing)

Leading to benefit-risk balance evaluation by regulators

Benefit-risk can be reviewed at any time

Are the standards different between children and adults?

In principle, no.

However, paediatric specificities

- Avoiding unnecessary trials means extrapolation of adult data where possible
- Safety data cannot be predicted from adults (e.g. valproate, diazepam, phenobarbital, propofol)
- Pharmacokinetics and pharmacodynamics vary due to growth/maturation (dose is different)

Child means children

Not a single population

- Adolescent (12-18 years)
- Child (2-11 years)
- Infant (1 month- 23 months)
- Newborn (term and pre-term) up to 28 days

- This internationally agreed classification does not match pharmacological stages

Ethical considerations for children

Children are a vulnerable population for clinical trials

- Legally cannot consent for research before 18 years (in EU, except Scotland which accepts 16)
- Vulnerability of the child in making decisions (susceptible to influence, limited understanding of research, unable to express will, neonates)
- Vulnerability of parents from countries where access to care is limited, conflicts of interests for researchers

Medicines must be studied in children

Ethical duty (for each of us) to progress science

Paediatricians must rely on evidence-based medicine

Protecting children involved in research

Need for more paediatric clinical trials but mostly better clinical trials*

Data must be published* and/or made available

*Consort-C 2010. Lancet 2010 Jul 24;376(9737):229-30.

In EU and US medicines are developed for children

In both regions, legal framework imposing paediatric development to pharmaceutical companies (since 2007 in EU*)

This ‘burden’ is compensated by extended patent protection (financial reward)

Development is ‘agreed’ with regulators

Hopefully, ‘global’ development for paediatric medicines

*Regulation (EC) No 1901/2006

EU Paediatric Investigation Plans

Include all measures and timelines for children from birth to 18 years:

- Paediatric formulations and pharmaceutical forms
- Non-clinical studies in juvenile animals (in particular for neonatal studies)
- Dose determination in all subsets
- Clinical demonstration of efficacy, where necessary (one study… in each subset?)
- Safety database and long term follow-up

Paediatric Committee

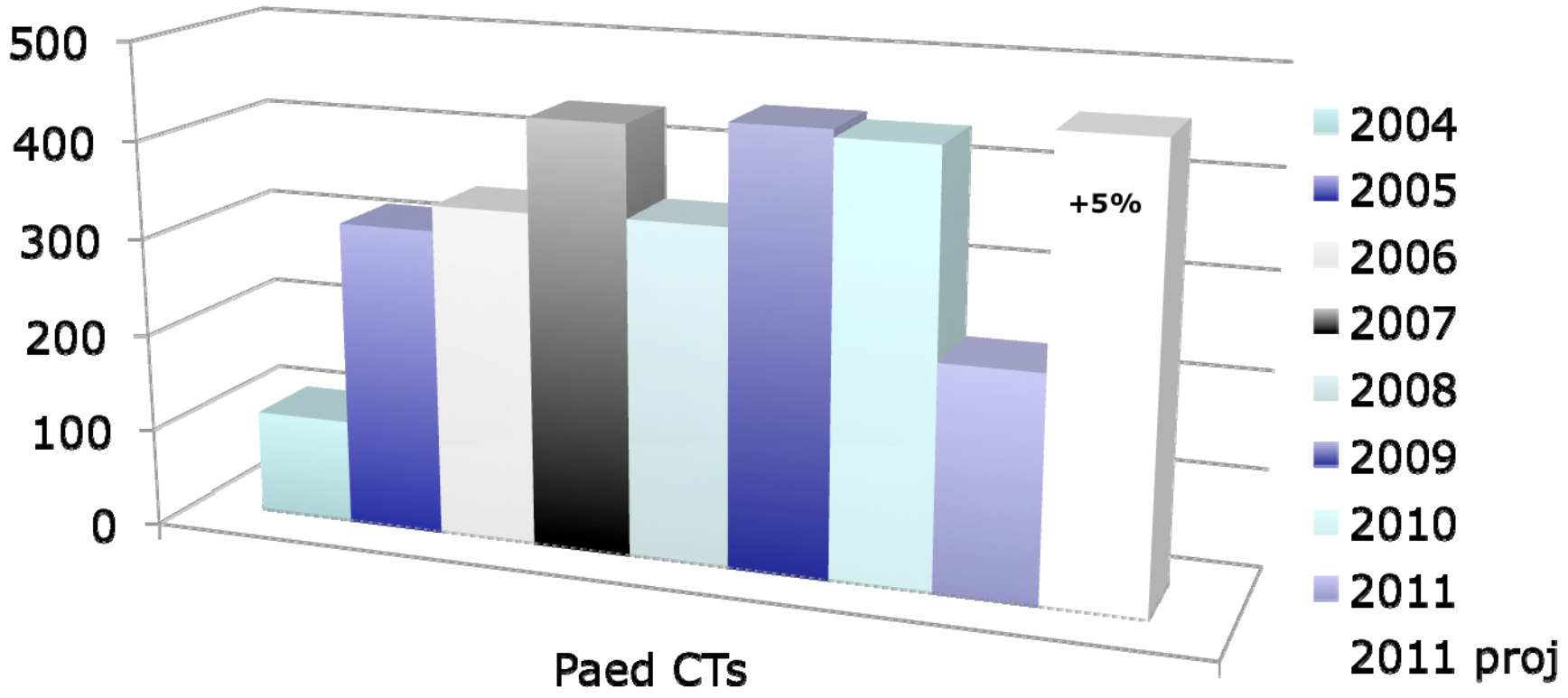
Agrees, modifies, or rejects plan proposed by companies

Waives development in children for lack of efficacy, lack of safety, lack of significant therapeutic benefit, when disease does not occur in children

Has seen more than 1100 plans or waivers (80% for new products) *but only about 50 new medicines per year in the world*

Early agreements of plans (during adult development) rather than early performance of trials

Paediatric Medicines Clinical Trials in EU (and outside)



EudraCT data: 2,508/29,625 total (8.5%)

Paediatric Committee and Plans (2007-9)

Deferrals of studies in 91% of cases for new medicines (103/113)

54 Plans: **Age groups**: neonatal studies proposed in 15%, but 26% requested by Paediatric Committee

Change in **numbers** of participants (increase in 9% and decrease in 15%)

54 plans proposing 62 ph II-III trials (23 added):

Design: 33/62 double blind, 39 controlled (35 active, 4 placebo)

Olski TM et al. Three years of Paediatric Regulation in EU. Eur J Clin Pharmacol 2011

Can we apply the adult standards?

Gaps in scientific knowledge:

- Pathophysiology
- Lack of outcome measures (e.g. heart failure)
- Lack of comparators

Methodological issues (some oppose placebo use in children)

Feasibility of trials (few children available for trials, competition between similar medicines)

Safety standards for adults?

- International recommendations for a new medicine (in order to detect rare adverse reactions)

1500 patients or subjects exposed

100 for a year if long-term use

- No similar recommendations for children (feasibility?)
- Long-term consequences of medicine use

Conclusions

It is about time paediatricians rely on evidence based medicine and therefore contribute to clinical trials!

Developing medicines for all ages is not an easy (nor cheap) task

Need for concerted efforts to progress science (from trial design to analysis of results) and make more medicines available to prescribers and children including neonates

Standards will evolve…