First-in-Children Clinical Trials

Background, Perspectives, Proposal

Ethics Working Group

European Academy of Paediatrics (EAP)

UEMS Section of Paediatrics

Vilamoura, Portugal

12 May 2017

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What is the current view from Europe on first-in-human clinical studies?

How should we consider, guide, and plan ‘first-in-children’ clinical trials?

The TeGenero 1412 Study

'Human guinea pig
Raste Khan'

The Sun 15-03-2006

TGN 1412 Placebo Group, TeGenero & Parexel CRO

TGN 1412 Background

- TeGenero AG: a privately held biopharmaceutical company engaged in developing therapeutic drugs for severe immunological disorders.
  Science Park Würzburg, Germany (since 2000)
- Parexel CRO (US firm)
- Northwick Park Hospital, northwest London
- first submitted as a Clinical Trial Application (CTA) in Germany, but approval delayed pending a request for further information from the Paul Ehrlich Institute

TGN 1412 Trial Design

- an immunomodulatory humanized agonistic anti-CD28 monoclonal antibody targeted at diseases such as multiple sclerosis, rheumatoid arthritis, and certain cancers
- ‘first-in-man’ study
- 8 volunteers (males - paid £2,000 each): 6 received the test drug, 2 received placebo
- Medicines and Healthcare Products Regulatory Agency (MHRA) approval
- local research ethics committee (REC) approval

TGN 1412 Result

- Adverse events: swelled heads and failed organs in 6 volunteers – 2 in critical conditions ('catastrophic multisystem failure' - BMJ)
- Duff Report + MHRA, UK, investigation
- Paul Ehrlich Institute, Germany, investigation
- Scotland Yard homicide division investigation
- Global press coverage (Sunday Times: 'Focus: poison chalice')
- BMJ Editorial: '*This experience should foster an open culture in medical research*'

TGN 1412 Outcomes

MHRA Report recommended:

- trials of immune drugs only on ill patients;
- centres be set up for riskier studies; and
- the first dose be given to one person at a time

(all official investigations into the study agreed that the rules had been followed and no blame was to be assigned)

Questions Addressed in Drafting a New EMA First-in Man Guideline

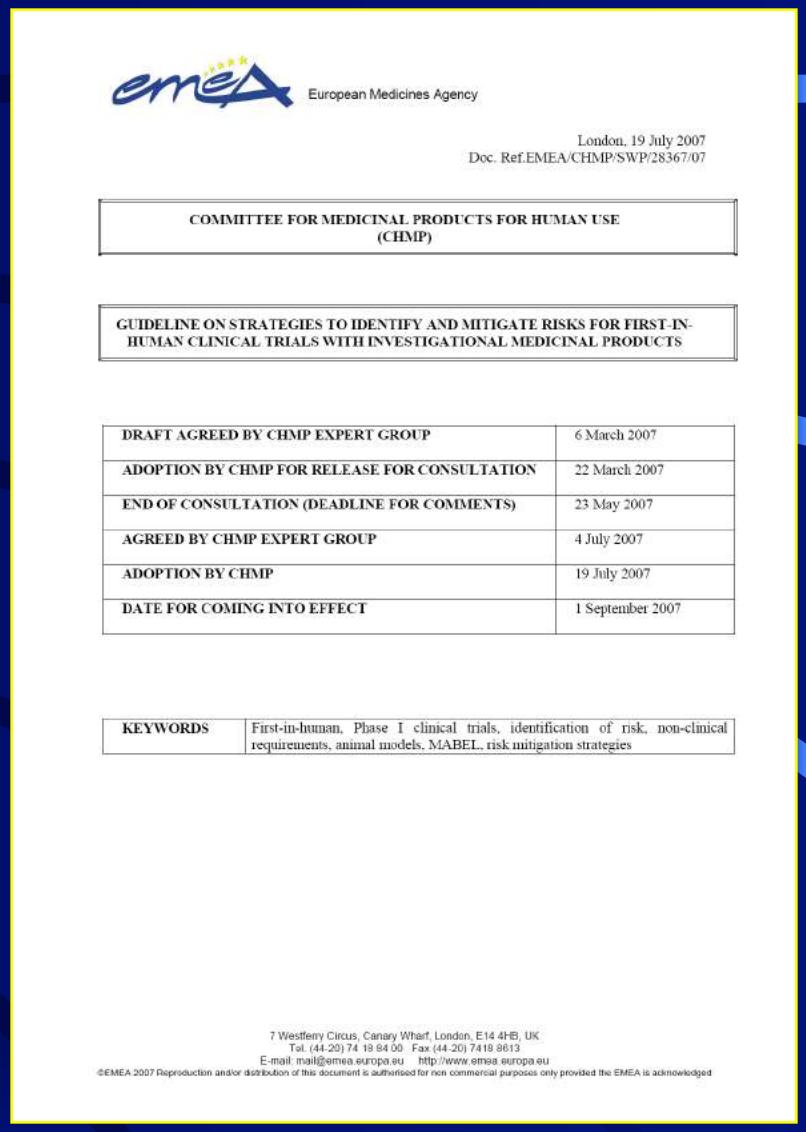
- Identifying risk appears possible, measuring risk appears difficult
- The need to expand guidelines beyond sponsors (e.g., regulatory agencies, investigators, ethics committees, patients)
- The role of animal models and disease models in measuring risk (e.g., MABEL)
- Dose escalation, ascending, and monitoring
- Use of patients vs. health volunteers

EMEA-CHMP Guideline

‘Guidelines on Strategies to Identify and Mitigate Risk First-in-humans Clinical Trials with Investigational Medicinal Products’

Adoption:
19 July 2007

Effective since:
1 September 2007



European Medicines Agency

London, 19 July 2007
Doc. Ref.EMEA/CHMP/SWP/28367/07

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

GUIDELINE ON STRATEGIES TO IDENTIFY AND MITIGATE RISKS FOR FIRST-IN-HUMAN CLINICAL TRIALS WITH INVESTIGATIONAL MEDICINAL PRODUCTS

DRAFT AGREED BY CHMP EXPERT GROUP	6 March 2007
ADOPTION BY CHMP FOR RELEASE FOR CONSULTATION	22 March 2007
END OF CONSULTATION (DEADLINE FOR COMMENTS)	23 May 2007
AGREED BY CHMP EXPERT GROUP	4 July 2007
ADOPTION BY CHMP	19 July 2007
DATE FOR COMING INTO EFFECT	1 September 2007

KEYWORDS	First-in-human, Phase I clinical trials, identification of risk, non-clinical requirements, animal models, MABEL, risk mitigation strategies

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BIA 10-2474 – Background

- Phase I double-blind, randomized, placebo-controlled, combined single and multiple ascending dose study in healthy volunteers (10 January 2016)
- A molecule that acts on the body's endocannabinoid system, intended to act on neuropathic pain
- Targeted conditions included ‘anxiety, mood disorders, and Parkinson's disease’.

BIA 10-2474 – Actors

- Centre Hospitalo-Universitaire de Rennes, France
- BIAL, Portuguese Pharmaceutical Company
- BIOTRIAL CRO specialized in early drug development
- l'ARS de Bretagne
- BIOTRIAL passed GCP and GLP inspections in 2014 performed by ANSM
- Comité compétent de protection des personnes qui se prêtent à des recherches biomédicales (CPP Ouest VI)

BIA 10-2474 – Events

- Previously 90 healthy volunteers had participated in parts of this Phase I study – no SAE's reported
- In this subsequent part of the protocol, groups of 8 healthy volunteers (6 active, 2 placebo) received ascending doses
- 1 volunteered died, 5 others hospitalized with serious adverse reactions

BIA 10-2474
IGAS Inquiry Report - Questions

- How was the trial authorized?
- Was the authorization process normal?
- Were recruitment procedures respected?
- How was the drug administered?
- How were the adverse events reported?
- How were the families informed of the adverse events?

BIA 10-2474
IGAS Inquiry Report – Findings

- No need to call into question the regulatory authority's and ethics committee's authorizations
- The regulatory authority should have asked for more scientific information on the dosing in the study
- The ethics committee had indicated that dosage should be better looked into, but this was not followed in the protocol

  'the latitude left to the investigator and sponsor did not provide for a sufficient framework for the protection of human subjects'

BIA 10-2474
IGAS Inquiry Report – Failures

1. The study should have been stopped when the first subject was hospitalized
2. The incident should have been reported immediately (not 4 days later)
3. All other subjects should have been notified immediately and asked if they wanted to continue

- The trial protocol provisions (for dosage) had been too vague, not precise enough

BIA 10-2474
IGAS Inquiry Report
Recommendations

- Improve the safety and quality of first-in-human protocols
- Improve the independence and quality of the work of the CPP (ethics committee)
- Improve the safety of the conduct of clinical trials
- Review the framework for reporting SAE's
- Review the alerting of SAE's in the field

EMA Proposals to Revise Guidance on First-in-Human Clinical Trials (21 July 2016)

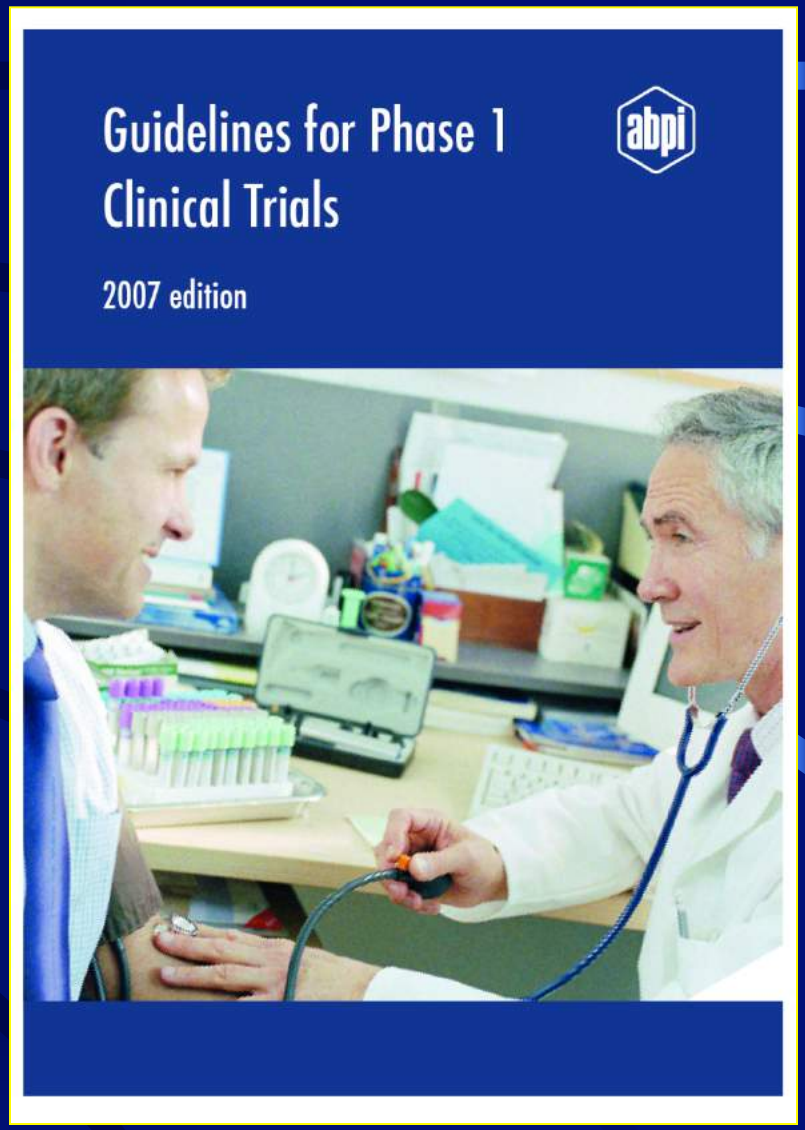
- First-in-human studies evolve toward a more integrated approach
- Sponsors including several steps in a single protocol
  - Assessing single and multiple ascending doses
  - Food interactions
  - Different age groups
- No discussion of first-in-children clinical trials

EMA Proposals to Revise Guidance on First-in-Human Clinical Trials (21 July 2016)

- Need for a structured approach to conduct these trials with incremental decisions on next steps based on the data collected at each previous step. [adaptive design]
- An approach designed for the specificities of each medicine, its mechanism of action, and intended therapeutic use. [microdosing, phase 0]

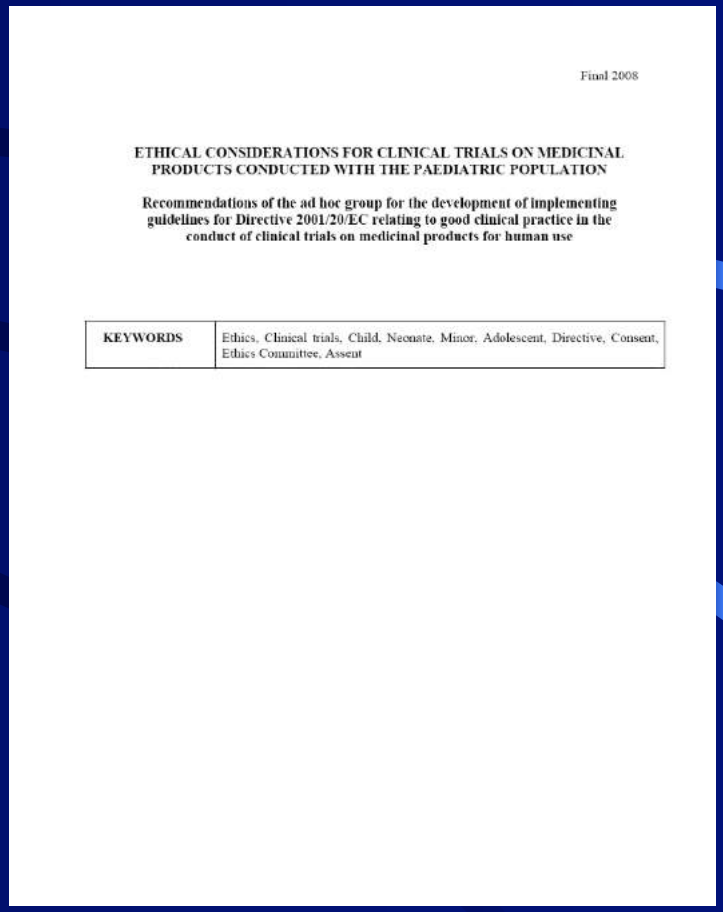
ABPI Phase I CT Guideline

- September 2007
- Foreword: Sir Gordon Duff
- Revision of the 1970, 1977, 1998 ABPI Guidelines
- Revision begun prior to the TGN1412 study



Ethical Considerations for Clinical Trials Conducted with the Paediatric Population (2008)

Recommendations of the Ad hoc group for the development of implementing guidelines for Directive 2001/20/EC relating to good clinical practice in the conduct of clinical trials on medicinal products for human use



Final 2008

ETHICAL CONSIDERATIONS FOR CLINICAL TRIALS ON MEDICINAL PRODUCTS CONDUCTED WITH THE PAEDIATRIC POPULATION

Recommendations of the ad hoc group for the development of implementing guidelines for Directive 2001/20/EC relating to good clinical practice in the conduct of clinical trials on medicinal products for human use

KEYWORDS	Ethics, Clinical trials, Child, Neonate, Minor, Adolescent, Directive, Consent, Ethics Committee, Assent

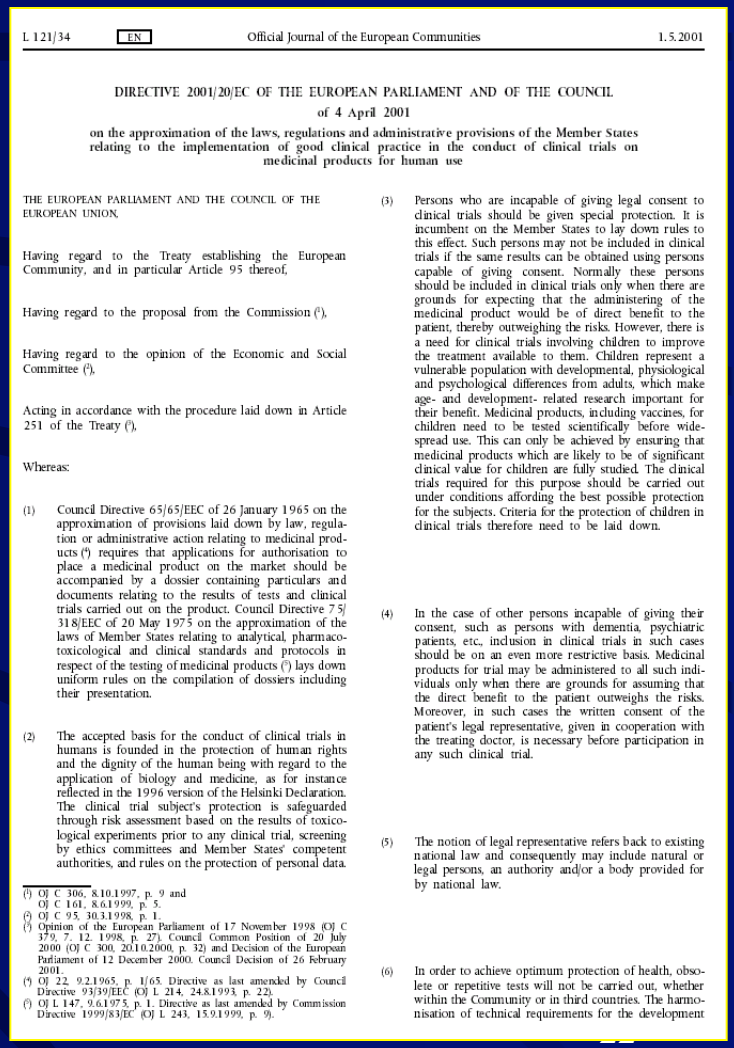
Children in Phase I Studies

15. Healthy children/ 'volunteers' studies

In principle, healthy children should not be enrolled as healthy volunteers, because they cannot consent and are vulnerable. Studies should not be performed in children when they can be performed in adults. In some situations however, studies have to be performed in healthy children. Prevention trials or paediatric vaccine trials, including immunogenicity studies, may fall into this category are an example of such trials. Whenever possible the older age groups should be considered for inclusion before the younger ones. Proof of concept should be obtained in relevant animal models and/or in adults whenever possible. Studies such as pharmacokinetic studies, which cannot be performed in adults, should be done in the intended population as far as possible, i.e., the one affected by the disease, although it is recognised that data obtained in affected children may have increased variability. Vaccines trials are performed in healthy children, but who represent the intended population.

EU Directive 2001/20/EC

'OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use'



L 121/34 EN Official Journal of the European Communities 1.5.2001

DIRECTIVE 2001/20/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL
of 4 April 2001
on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use

THE EUROPEAN PARLIAMENT AND THE COUNCIL OF THE EUROPEAN UNION,

Having regard to the Treaty establishing the European Community, and in particular Article 95 thereof,

Having regard to the proposal from the Commission (1),

Having regard to the opinion of the Economic and Social Committee (2),

Acting in accordance with the procedure laid down in Article 251 of the Treaty (3),

Whereas:

(1) Council Directive 65/65/EEC of 26 January 1965 on the approximation of provisions laid down by law, regulation or administrative action relating to medicinal products (4) requires that applications for authorisation to place a medicinal product on the market should be accompanied by a dossier containing particulars and documents relating to the results of tests and clinical trials carried out on the product. Council Directive 75/318/EEC of 20 May 1975 on the approximation of the laws of Member States relating to analytical, pharmaco-toxicological and clinical standards and protocols in respect of the testing of medicinal products (5) lays down uniform rules on the compilation of dossiers including their presentation.

(2) The accepted basis for the conduct of clinical trials in humans is founded in the protection of human rights and the dignity of the human being with regard to the application of biology and medicine, as for instance reflected in the 1996 version of the Helsinki Declaration. The clinical trial subject's protection is safeguarded through risk assessment based on the results of toxicological experiments prior to any clinical trial, screening by ethics committees and Member States' competent authorities, and rules on the protection of personal data.

(3) Persons who are incapable of giving legal consent to clinical trials should be given special protection. It is incumbent on the Member States to lay down rules to this effect. Such persons may not be included in clinical trials if the same results can be obtained using persons capable of giving consent. Normally these persons should be included in clinical trials only when there are grounds for expecting that the administering of the medicinal product would be of direct benefit to the patient, thereby outweighing the risks. However, there is a need for clinical trials involving children to improve the treatment available to them. Children represent a vulnerable population with developmental, physiological and psychological differences from adults, which make age- and development- related research important for their benefit. Medicinal products, including vaccines, for children need to be tested scientifically before widespread use. This can only be achieved by ensuring that medicinal products which are likely to be of significant clinical value for children are fully studied. The clinical trials required for this purpose should be carried out under conditions affording the best possible protection for the subjects. Criteria for the protection of children in clinical trials therefore need to be laid down.

(4) In the case of other persons incapable of giving their consent, such as persons with dementia, psychiatric patients, etc., inclusion in clinical trials in such cases should be on an even more restrictive basis. Medicinal products for trial may be administered to all such individuals only when there are grounds for assuming that the direct benefit to the patient outweighs the risks. Moreover, in such cases the written consent of the patient's legal representative, given in cooperation with the treating doctor, is necessary before participation in any such clinical trial.

(5) The notion of legal representative refers back to existing national law and consequently may include natural or legal persons, an authority and/or a body provided for by national law.

(6) In order to achieve optimum protection of health, obsolete or repetitive tests will not be carried out, whether within the Community or in third countries. The harmonisation of technical requirements for the development

(1) OJ C 306, 8.10.1997, p. 9 and OJ C 161, 8.6.1999, p. 5.
(2) OJ C 95, 30.3.1998, p. 1.
(3) Opinion of the European Parliament of 17 November 1998 (OJ C 379, 7. 12. 1998, p. 27). Council Common Position of 20 July 2000 (OJ C 300, 20.10.2000, p. 32) and Decision of the European Parliament of 12 December 2000. Council Decision of 26 February 2001.
(4) OJ 22, 9.2.1965, p. 1/65. Directive as last amended by Council Directive 93/39/EEC (OJ L 214, 24.8.1993, p. 22).
(5) OJ L 147, 9.6.1975, p. 1. Directive as last amended by Commission Directive 1999/83/EC (OJ L 243, 15.9.1999, p. 9).

EU Paediatric Regulation

- To ensure high quality research into the development of medicines for children.
- To ensure, over time, that the majority of medicines used by children are specifically authorised for such use.
- To ensure the availability of high quality information about medicines used by children.

27.12.2006 EN Official Journal of the European Union L 378/1

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(Acts whose publication is obligatory)

REGULATION (EC) No 1901/2006 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

of 12 December 2006

on medicinal products for paediatric use and amending Regulation (EEC) No 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004

(Text with EEA relevance)

THE EUROPEAN PARLIAMENT AND THE COUNCIL OF THE EUROPEAN UNION,

Having regard to the Treaty establishing the European Community, and in particular Article 95 thereof,

Having regard to the proposal from the Commission,

Having regard to the Opinion of the European Economic and Social Committee [1],

Having consulted the Committee of the Regions,

Acting in accordance with the procedure referred to in Article 251 of the Treaty [2],

Whereas:

(1) Before a medicinal product for human use is placed on the market in one or more Member States, it generally has to have undergone extensive studies, including preclinical tests and clinical trials, to ensure that it is safe, of high quality and effective for use in the target population.

(2) Such studies may not have been undertaken for use in the paediatric population and many of the medicinal products currently used to treat the paediatric population have not been studied or authorised for such use. Market forces alone have proven insufficient to stimulate adequate research into, and the development and authorisation of, medicinal products for the paediatric population.

(3) Problems resulting from the absence of suitably adapted medicinal products for the paediatric population include inadequate dosage information which leads to increased risks of adverse reactions including death, ineffective treatment through under-dosage, non-availability to the paediatric population of therapeutic advances, suitable formulations and routes of administration, as well as use of magistral or officinal formulations to treat the paediatric population which may be of poor quality.

(4) This Regulation aims to facilitate the development and accessibility of medicinal products for use in the paediatric population, to ensure that medicinal products used to treat the paediatric population are subject to ethical research of high quality and are appropriately authorised for use in the paediatric population, and to improve the information available on the use of medicinal products in the various paediatric populations. These objectives should be achieved without subjecting the paediatric population to unnecessary clinical trials and without delaying the authorisation of medicinal products for other age populations.

(5) While taking into account the fact that the regulation of medicinal products must be fundamentally aimed at safeguarding public health, this aim must be achieved by means that do not impede the free movement of safe medicinal products within the Community. The differences between the national legislative, regulatory and administrative provisions on medicinal products tend to hinder intra-Community trade and therefore directly affect the operation of the internal market. Any action to promote the development and authorisation of medicinal products for paediatric use is therefore justified with a view to preventing or eliminating these obstacles. Article 95 of the Treaty is therefore the proper legal basis.

(6) The establishment of a system of both obligations and rewards and incentives has proved necessary to achieve these objectives. The precise nature of these obligations and rewards and incentives should take account of the status of the particular medicinal product concerned. This Regulation should apply to all the medicinal products required for paediatric use and therefore its scope should cover products under development and yet-to-be authorised, authorised products covered by intellectual property rights and authorised products no longer covered by intellectual property rights.

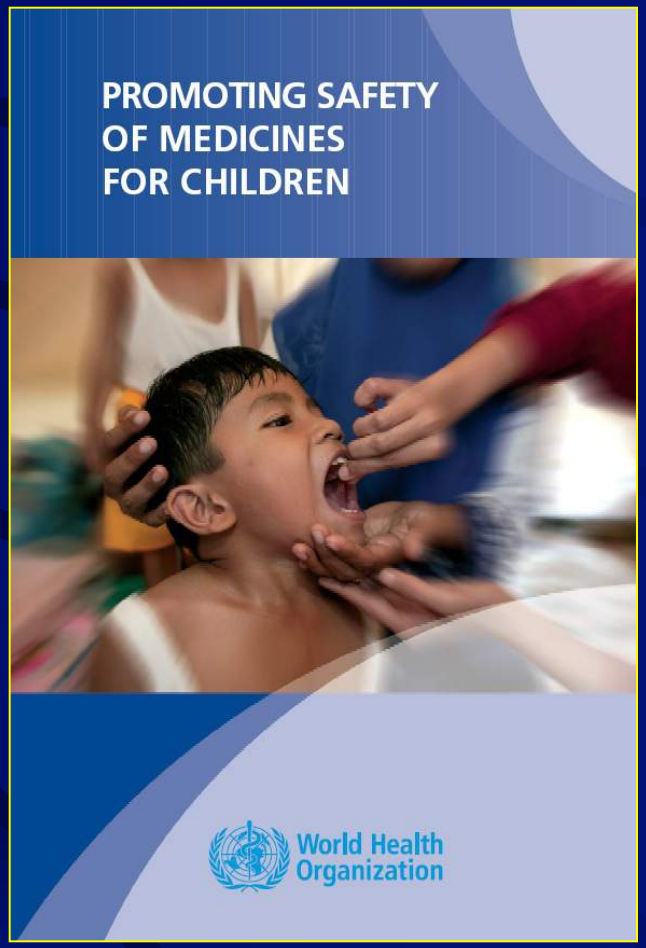
[1] OJ C 267, 27.10.2005, p. 1.

[2] Opinion of the European Parliament of 7 September 2005 (OJ C 193 E, 17.8.2006, p. 225), Council Common Position of 10 March 2006 (OJ C 132 E, 7.6.2006, p. 1) and Position of the European Parliament of 1 June 2006 (not yet published in the Official Journal). Council Decision of 23 October 2006.

A Growing Global Interest in Paediatric Medicines Development

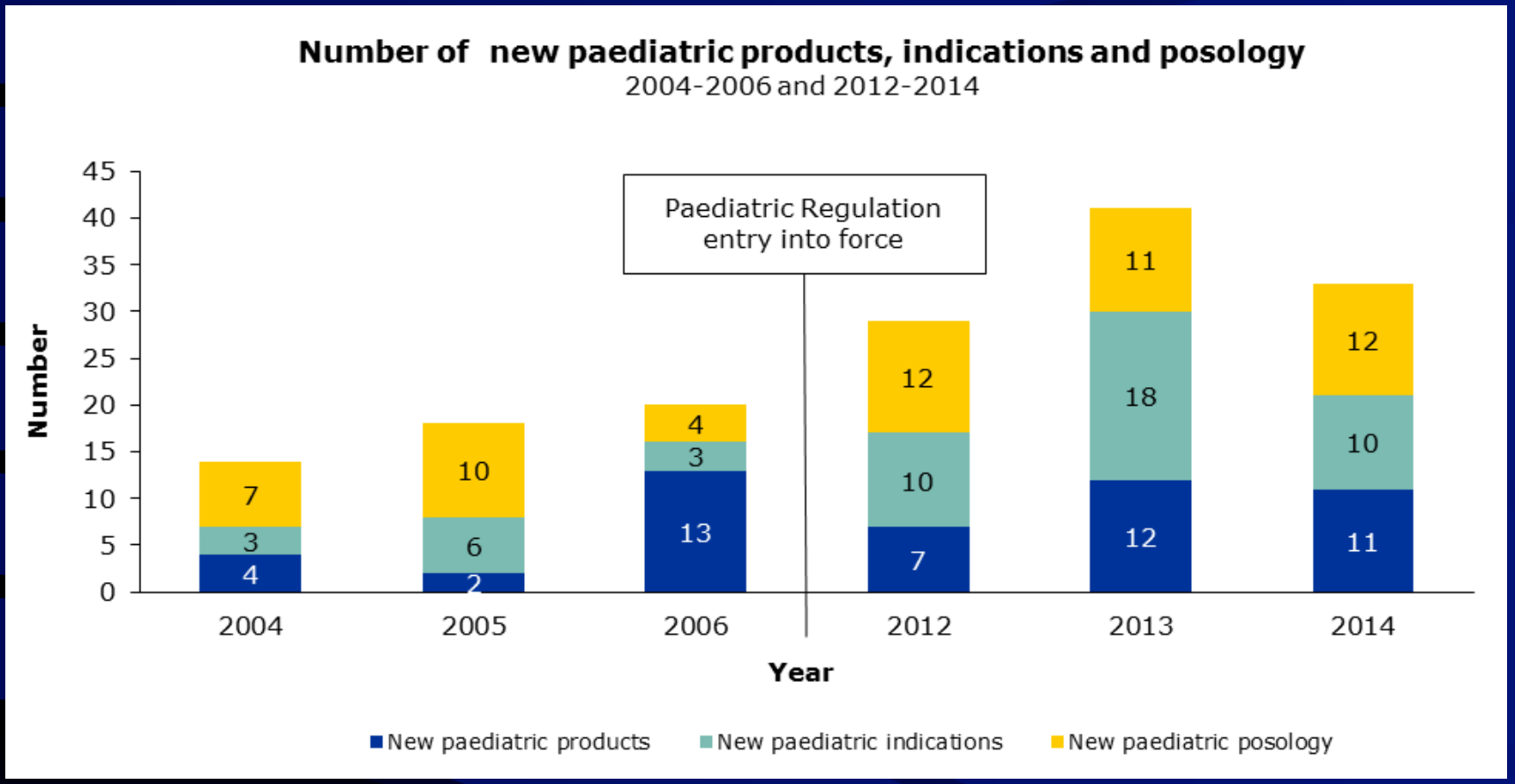
- WHO International Network on Paediatric Medicines

  Chaired by the EMA, Dr. Agnès Saint Raymond



Lessons Learned from the Paediatric Regulation

- The PR was a success:
  - 2007-2015, 238 new paediatric medicines and indications (141), the majority through the centralized procedure
  - 2007-2015, 39 new paediatric pharmaceutical forms
  - End 2015, PDCO had adopted opinions on final/full compliance for 99 PIPs



Number of centrally authorised products (CAPs) becoming available for children in 2004-2006 and 2012-2014 (new initial marketing authorisations, new paediatric indications (SmPC Section 4.1) or new posology information (SmPC Section 4.2) for already authorised products.

Building Infrastructure for Paediatric Trials through the PR

- Enpr-EMA - European network of paediatric research at the European Medicines Agency
  - Strong representation in Western Europe, weak in Eastern Europe (Slovenia, Poland, EAP)
- PUMA - Paediatric Use Marketing Authorisation
  - only 2 products approved in 10 years, not a success

Some Challenges for the PR

- Difficult to develop and exercise Paediatric Investigation Plans (PIPs) in all age categories
- By the end of 2015, National Patent Offices (NPO) in 23 Member States reported as having granted or pending 322 six-month extensions of the SPC for 39 medicines
- Not all medicines developed under PIPs make it to the market.

Ethical considerations for clinical trials on medicinal products conducted with minors

EMA Consultation Document 1 June 2016

‘Therapeutic confirmatory ("phase III") drug trials are the best-known examples of research belonging to this category [‘direct benefit’ to the minor]. However, depending on the design, early phase drug trials may also offer the prospect of direct benefit. During the benefit-risk assessment of the trial, the expected direct benefit of the intervention(s) should outweigh the risks and expected burdens.

Addendum to ICH E11: Clinical Investigation of Medicinal Products in the Pediatric Population, 2016

- Addendum to the ICH E11 (2000): Clinical Investigation of Medicinal Products in the Paediatric Population E11(R1)
- Current *Step 1* version dated 25 August 2016
- 'The purpose of the addendum is to complement and provide clarification and current regulatory perspective on topics in pediatric drug development.'

Addendum to ICH E11: Clinical Investigation of Medicinal Products in the Pediatric Population (2016)

- Section 2: Ethical Considerations (relevance, burden, assent)
- Section 3: Commonality of Scientific Approach for Pediatric Drug Development Programs (scientific approaches to multiregional pediatric drug development programs)
- Section 4: Age Classification and Pediatric Subgroups including Neonates
- Section 5: Approaches to Optimize Drug Development (Extrapolation; Modeling and Simulation)
- Section 6: Practicalities in the Design and Execution of Pediatric Clinical Trials: (Feasibility, Outcomes Assessment, Long-term Clinical Aspects, including Safety)
- Section 7: Pediatric Formulations (Dosage and Administration, Excipients, Palatability and Acceptability, Neonates)
- Section 8: Glossary

Rethinking Paediatric Clinical Trials

- Children are biologically not simply 'small adults', often having a different metabolism profile than adults, and thus a (potentially) different pharmacokinetic (ADME) and pharmacodynamic profile regarding specific medicines.
- Children have been considered 'orphans' of medical research. Children need to be provided specific scientifically sound and ethically acceptable pathways to medical testing across their age groups.
- This pathways need to begin with the first clinical studies in children (whether or not similar studies have already been carried out in adults) and across all (chronological/ biological) age groups.

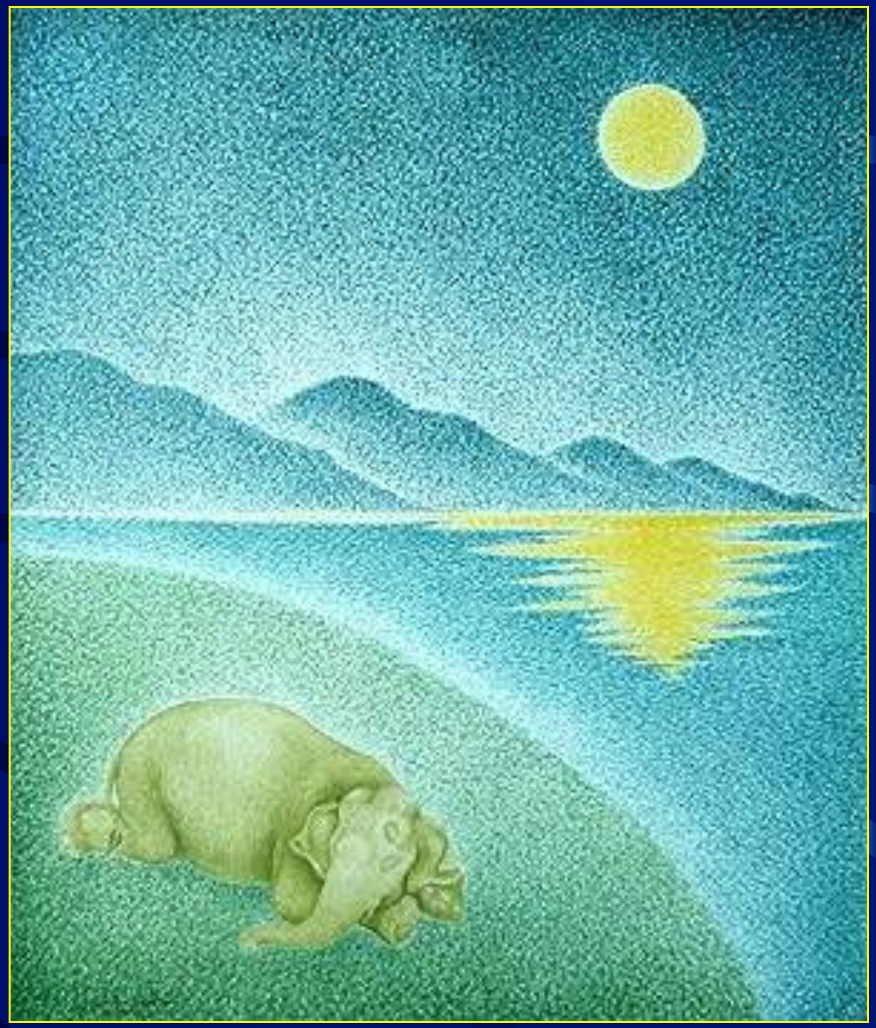
First-in-Children Clinical Trials Guidance (1)

- A new concept of 'first-in-children clinical trials' separated from 'phase I clinical trials (in children)'
- A clear description of specific scientifically sound and ethically acceptable pathways
- Guidance on pharmacokinetic studies in children (including defining appropriate animal models, defining appropriate ADME (absorption, distribution, metabolism, and excretion] studies, the use of MIST [metabolites in safety testing] studies, and the definition of MABEL guidance [minimum anticipated biological effect level] for first dose in children])

First-in-Children Clinical Trials Guidance (2)

- Guidance on paediatric age and subgroups classification – the relationship between chronological age and biological age, supported by guidance on defining biological age subgroups
- What are the defining moments for first-in-children studies: specifically, what information/data is needed prior to the introduction of a medicine into the paediatric population
- Defining appropriate criteria for Phase 0 and Phase I clinical trials in children
- Defining criteria for dose escalation studies in children
- Defining criteria for early phase vaccine studies in children
- Identifying pharmaco-dynamic and therapeutic targets for 'first-in-children' clinical trials of medicinal products

How can we create and ensure a scientifically reliable and safe clinical trial environment for first-in-children studies?



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