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A Summary of the EU Paediatric Initiatives

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The views in this presentation are those of the author and should not be understood or quoted as being made on behalf of any regulatory body and/or its scientific committees

About 22% of the EU population, i.e. over 100 million people, aged less than 19 yr

Milestones on the way to the EU Paediatric regulation

- EC Round Table, European Medicines Agency (EMEA) - 18 December 1997
- EU Council resolution - 14 December 2000
- Public consultations - 2002 and 2004
- EU Commission proposal -29 September 2004
- European Parliament 1. vote - 7. Sept. 2005
- Adoption by EU Council - 9 December 2005
- 2nd vote and adoption by EP - 1. June 2006
- Entry into force/operative - 26. January 2007

Overall objectives of the Regulation

- To **improve the health of the children** of Europe by increasing the research, development and authorisation of medicines for use in children
- *Without subjecting children to unnecessary clinical trials*
- *Without delaying the authorisation of medicinal products for other age populations*

General objectives

- Facilitate the **development and accessibility** of medicines for use in children
- Ensure that medicines used to treat children are **subject to high quality ethical research**
- Ensure that medicines used to treat children are **appropriately authorised** for use in children
- **Improve the information** available on the use of medicines in various paediatric populations

Requirements

- A **requirement** at the time of marketing authorisation applications **for data** on the use of the medicine **in children** resulting from an agreed *Paediatric Investigation Plan (PIP)*
- System of **waivers** from the requirement for medicines unlikely to benefit children
- System of **deferrals** of the timing of the requirement to ensure medicines are tested in children only when it is safe to do so and to prevent the requirements delaying the authorisation of medicines for adults

Rewards and incentives

- For compliance with the requirement in the form of 6 months extension to the supplementary protection certificate (in effect, 6 month patent extension)
- For orphan medicines, an incentive for compliance with the requirement in the form of an additional 2 years of market exclusivity added to the existing 10 years awarded under the EU orphan regulation

- New type of marketing authorisation, the Paediatric Use Marketing Authorisation (PUMA), which allows ten-years of data protection for innovation (new studies) on off-patent products

Support measures

- A commitment to EU funding into studies on off-patent medicines for children
- Establishment of an expert committee, the Paediatric Committee (PDCO) within the EMEA
- Measures to increase the robustness of pharmacovigilance for medicines for children
- EU inventory of the therapeutic needs of children to focus research, development and authorisation of medicines
- EU network of investigators and trial centres to conduct the research and development required
- Free scientific advice for the industry, by the EMEA
- Publicly available database of paediatric studies

The requirement for new medicines

- Marketing Authorisation Application (MAA) considered valid only if it includes one of the following:
  - **Results of all studies** performed and details of all information collected in compliance with an agreed PIP
  - A product-specific **waiver** or a class **waiver**
  - A **deferral**
- The PIP also to be included in the application
- The documents submitted to cover **all subsets of the paediatric population**

Medicinal Products subject to the requirement

- Authorised medicinal products protected either by a Supplementary protection certificate (SPC) or a patent which qualifies for the granting of the SPC
- New medicinal products (not authorised)
- Medicinal products already authorised
  - Applications for authorisation of new indications, new pharmaceutical forms, and new routes of administration
  - Requirement covers both the existing and the new indications, pharmaceutical forms and routes of administration

Requirement excludes Marketing Authorisation Application (MAA) for

- Generics or similar biological medicinal products
- Medicinal products authorised through the well-established medicinal use procedure
- Homeopathic medicinal products and traditional herbal medicinal products authorised

through the simplified registration procedures

Extension of Supplementary protection certificate (SPC) by 6 months if

- **All the measures** included in the agreed paediatric investigation plan are **complied with**
- Product **authorised in all Member States**
- **Relevant information** on the results of studies **included in product information**
- *Note:* Reward granted even when completion of the agreed PIP fails to lead to the authorisation of a paediatric indication, but the results of the studies conducted are reflected in the Summary Of Product Characteristics (SPC) and, if appropriate, in the package leaflet

Paediatric Use Marketing Authorisation (PUMA)

- Incentive for authorised products no longer covered by intellectual property rights
- For medicinal products developed exclusively for use in the paediatric population
- Can retain the existing brand name to capitalise on existing brand recognition, while benefiting from the data exclusivity associated with a new marketing authorisation (10 years)
- Fee Scientific Advice
- Application to include data concerning use of the product in the paediatric population, collected in accordance with an agreed PIP
- Including data needed to support an appropriate strength, pharmaceutical form or route of administration for the product
- Data may be derived from published literature or from new studies
- Also able to refer to data contained in the dossier of a MP authorised in the Community

Paediatric Investigation Plan (PIP)

- Document upon which the development and authorisation of medicinal products for the paediatric population should be based
- The PIP to specify the timing and the measures proposed to demonstrate the quality, safety and efficacy of the medicinal product
- In all subsets of the paediatric population that may be concerned
- Describe any measures to adapt the formulation of the medicinal product so as to make its use more acceptable, easier, safer or more effective for different subsets of the paediatric population
- To be submitted <u>early</u> (unless otherwise justified)
  - Not later than upon completion of the pharmacokinetic studies in adults
- Opinion of Paediatric Committee whether or not
  - Proposed studies will ensure the generation of the necessary data determining the conditions in which the medicinal product may be used to treat the paediatric population or subsets thereof

- Expected therapeutic benefits justify the studies proposed
- Measures proposed to adapt the formulation of the medicinal product for use in different subsets of the paediatric population are appropriate

Paediatric Committee

- Independent scientific committee within EMEA
- Composed of 33 Members and alternates
  - 5 members appointed by the Committee for Medicinal Products for Human Use (CHMP)
  - 1 member appointed by each of the MS whose national competent authority not represented through the members appointed by the CHMP
  - 6 appointed by the Commission based on a public call for expressions of interest, and after consulting the European Parliament
    - 3 to represent health professionals
    - 3 to represent patient associations

Tasks of Paediatric Committee

- Assessment of content of any submitted PIP
- Assessment of Waivers and Deferrals
- On request evaluate compliance of MAA with PIP
- On request evaluate data on quality, safety and efficacy for use in the paediatric population
- Support and advise the EMEA on establishing the European network
- Provide advice on any question related to medicinal products for paediatric use for EMEA and the Commission

Establishment of an European Paediatric Clinical Trials Network

- EMEA to develop a European network of Existing national and European networks, investigators and centres with specific expertise in performance of studies in paediatric population
- Objectives of the European network:
- To coordinate studies relating to paediatric medicinal products
- To build up the necessary scientific and administrative competences at European level
- To avoid duplication of studies in children
- Compatibility with the work of strengthening the European Research Area in the context of the Community Framework Programs
- To benefit the paediatric population
- To act as a resource for industry
- Adoption of implementing strategy for launching and operation of the European network

by Management Board of EMEA within 1 year of the entry into force of Regulation

Community funding for research

- Funds for research into medicinal products for the paediatric population shall be provided for in the Community budget in order to support studies relating to medicinal products or active substances not covered by a patent or a supplementary protection certificate
- Funding delivered through the Community Framework Programmes or any other Community initiatives for the funding of research

Communication and coordination

- EMEA shall make public part of the information on paediatric clinical trials entered in the European database
  - Details of results of all trials contained in an agreed PIP and of any other trials submitted to competent authorities to be made public, whether or not trial was terminated prematurely
- Any paediatric studies already completed, by the date of entry into force, for products authorised in EU to be submitted for assessment to the competent authority
  - The competent authority may update the SPC and package leaflet, and may vary the MA accordingly
- Inventory of therapeutic needs
- Survey by Member States of 'all existing uses' of paediatric indications followed by report prepared by EMEA

Timelines from date of entry into force

- Regulation entered into force 26.1.2007
- Paediatric Committee to be established by 26.7.2007
- Paediatric Use Marketing Authorisation (PUMA) 26.7.2007
- Requirement for unauthorised MP's 26.7.2008
- Requirement for authorised protected MP's 26.1.2009
- Data on paediatric studies already completed to be submitted to competent authorities by 26.10.2010

Money matters (Data from Extended Impact Assessment)

- Estimated cots of testing medicines for children
  - 4 million € / product
- Estimated industry profit from 6 months SPC extension
  - 0.8 - 9.1 million € / product
- Estimated loss of profit for generics industry
  - 4 -51 million € across the entire sector
- Increase of EU pharmaceutical expenditure

- 0.06 - 0.25 % annually

Further information and documents

- EU Commission, DG Enterprise
  - http://ec.europa.eu/enterprise/pharmaceuticals/paediatrics/index.htm

- European Medicines Agency (EMEA)
  - http://www.emea.europa.eu

  - http://www.emea.europa.eu/htms/human/peg/pegfaq.htm

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Comparison of the US and EU paediatric initiatives

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Table 1: The Paediatric Initiatives in US and EU for products covered by intellectual property rights or exclusivity marketing rights

	US	EU
Legislation	FDA Modernization Act of 1997 (expired in 2002) , Best Pharmaceuticals for Children Act of 2002 (BPCA) Section 4 Pediatric Research Equity Act from 2003 (PREA)	EU Paediatric regulation (1901/2006)
In force	BPCA 2002-2007, PREA (2003-2007), New legislation is pending	2007-
Voluntary/mandatory	BPCA-voluntary, PREA-mandatory unless waiver granted	Paediatric development required (unless waiver granted)
Includes	BPCA and PREA-Products with remaining patents or exclusivity marketing rights PREA is limited to: 1) when the disease or condition is similar in adults and children, AND 2) if either widespread use is anticipated, OR 3) the product is considered a therapeutic advance	All new and authorized MPs protected either by a Supplemental Protection Certificate or a patent which qualifies for the granting of the Supplemental Protection Certificate (unless Waiver)
Excludes	BPCA and PREA-generics BPCA-biologicals and some antibiotics PREA-orphan products	Generics or similar biological MPs, MPs authorised through the well-established medicinal use procedure, homeopathic and traditional herbal MPs
When	BPCA-Before or after MAA as long as some patent or exclusivity protection is in effect PREA-Before MAA unless deferral granted	Before MAA or Application for Extension (unless deferral granted)
Agreement defining what needs to be done for incentive/reward	BPCA-Written Request from FDA PREA-Pediatric Investigation Plan (PIP) to be submitted to FDA	Paediatric Investigation Plan (PIP)
How	BPCA-Written request for BPCA issued by FDA, can be initiated by a proposal from the company ("Proposed Pediatric Study Request" ="PPSR") PREA- Mandatory to submit an agreed PIP and the results of the studies in the PIP at the time of submitting MAA (unless waiver or deferral granted)	Mandatory to submit an agreed PIP and the results of the studies in the PIP at the time of submitting MAA, otherwise MAA considered not valid (unless waiver or deferral granted)

	US	EU
What needs to be done	BPCA-Clinical studies and relevant preclinical data and formulation development based on perceived public health need PREA-Full development (clinical studies, formulation, all relevant age groups)	Full development (studies, formulation, all relevant age groups)
Orphan drugs/MPs	BPCA-Included PREA-Exempt	Included (requirement for those covered by intellectual property rights / voluntary for non-protected)
Incentive	BPCA-Incentive: 6 mo exclusivity for most eligible products and 2.5 years for Orphan Products (2 years Orphan Exclusivity plus 6 months pediatric exclusivity) PREA-None (Product may qualify for BPCA incentive while complying with PREA)	Reward: 6 mo extension of Supplemental Protection Certificate, Orphan MPs 2 yrs additional extension of exclusivity (to 12 yrs total)
Penalty	BPCA-None PREA-Absent pediatric information product can be considered misbranded and potentially withdrawn from the market	Financial penalties for infringement through the procedure laid down in Regulation (EC) No 726/2004. Names of anyone infringing, the amounts of and reasons for the financial penalties imposed to be made public
Information dissemination	BPCA-label change expected but not mandatory, publication of summary of FDA clinical and pharmacology reviews on Internet, publication of full FDA clinical and pharmacology reviews if new or supplemental MAA PREA-label change, publication of full FDA clinical and pharmacology reviews on Internet	Results of all studies to be included in the summary of product characteristics and, if appropriate, in the package leaflet of the medicinal product, provided that the competent authority deems the information to be of use to patients, whether or not all paediatric indications were approved. EPARs published on Internet by EMEA

BPCA=Best Pharmaceuticals for Children Act; PREA=Pediatric Research Equity Act; MP= Medicinal Product; SPC= Supplemental Protection Certificate; MAA= Market Authorization Application; FDA=Food and Drug Administration; PIP=Paediatric Investigation Plan; EPAR=European Public Assessment Report; EMEA=European Medicines Agency

Table 2: The Paediatric Initiatives in US and EU for Products not covered by intellectual property or marketing exclusivity rights

	US	EU
Legislation	BPCA Section 3	EU Paediatric regulation (1901/2006)
In force	2002-2007 (New legislation pending)	2007-
Instrument	Written Request from FDA- if declined by manufacturer then Request for Proposals for contract with National Institute of Health (NIH)	Paediatric Use Marketing Authorisation (PUMA)
Voluntary-mandatory	Voluntary	Voluntary
Invoked	For medicinal products no longer covered by intellectual property rights	For medicinal products no longer covered by intellectual property rights developed exclusively for use in the paediatric population
Includes	All authorized MPs but based on priority list	All authorized MPs
Orphan drugs/Orphan MPs	Eligible	Not eligible for PUMA, may get same reward for paediatric development as Orphan MPs covered by intellectual property rights
What needs to be done	Studies and, if required, formulation	Studies and paediatric formulation, based on Paediatric Investigation Plan (PIP)
Incentive	None	Main: 10-yr data protection for innovation In addition: Free Scientific Advice, access to Centralized Procedure, composite MAA, can retain existing brand name

BPCA=Best Pharmaceuticals for Children Act; FDA=Food and Drug Administration; PUMA=Paediatric Use Marketing Authorisation; MP= Medicinal Product;MAA= Market Authorization Application

Table 3: Some additional measures of the Paediatric Initiatives in US and EU

	US	EU
Funding for 'off-patent' medicines	If industry declines to perform studies, public funds (NIH)	EU Framework Programs starting with FP7 in 2007
Priority list	For 'off-patent' medicines	For 'off-patent' medicines
Research networks	Contracts with qualified facilities	Coordination of European Network
Information measures	Data available publicly Label change Publication of studies in peer reviewed literature	Publicly available database of paediatric studies, including details of results of all trials contained in an agreed PIP and of any other trials submitted to competent authorities
Other	Free scientific advice for the industry for on patent products from the FDA Free scientific advice for investigators for off patent products from NIH	Free scientific advice for the industry, by the EMEA
		Paediatric Committee (PDCO), independent scientific committee within EMEA to assess content of any submitted PIP, decide on Waivers and Deferrals. Provide advice on any question related to medicinal products for paediatric use for EMEA and the EU Commission
		Any paediatric studies already completed, by the date of entry into force of Regulation, for products authorised in EU to be submitted for assessment to the competent authority. The competent authority may update the Summary of Product Characteristics and package leaflet, and may vary the MA accordingly

NIH= National Institutes of Health; FP7=7th Framework Program for research and technological development; PIP=Paediatric Investigation Plan; EMEA=European Medicines Agency; FDA=Food and Drug Administration; MA=Marketing Authorisation