PAINEL III - MEDICAMENTOS E PEDIATRIA

ENSAIOS CLÍNICOS EM PEDIATRIA

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ENSAIOS CLÍNICOS EM PEDIATRIA

1. CICLO DE VIDA DO MEDICAMENTO
2. REALIDADE NACIONAL NOS ENSAIOS CLÍNICOS
3. DESENVOLVIMENTO DE FÁRMACOS EM PEDIATRIA
4. REGULAÇÃO EUROPEIA
5. IDEIAS-CHAVE

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CICLO DE VIDA DO MEDICAMENTO

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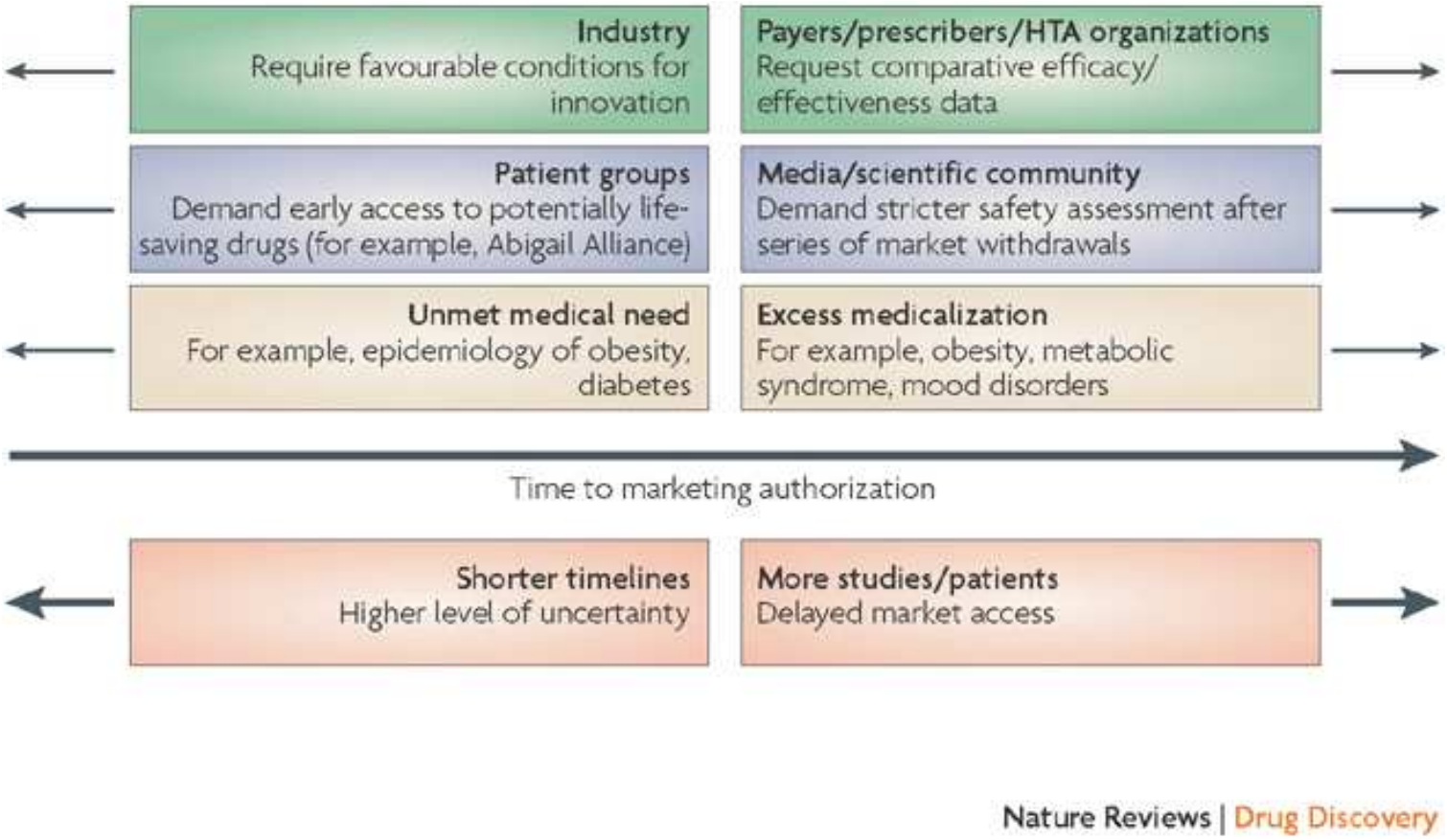
Fases do Estudo de um Fármaco

- Estudos Pré-Clinicos
  - Químicos; Biológicos; Animais
- Estudos Clínicos
  - Fase I (**farmacocinética** / intervalo de doses / efeitos / toxicidade)
  - Fase II (doses / **Eficácia e Segurança**)
  - Fase III (+**RCT**) (Eficácia e Segurança / Qualidade de Vida / adesão)

AIM

  - Fase IV (**Efectividade** / Segurança / marketing)

INTRODUÇÃO DO MEDICAMENTO NO MERCADO: QUANDO?



Eichler HG, Pignatti F, Flamion B, Leufkens H, Breckenridge A. Nat Drug Discov 2008; 7: 818-26.

Key issues in the lifecycle of a medicine

Question	Today's challenges
Robust definition and diagnosis of disease?	Psychiatric morbidities, somatic functional disorders, sepsis
Clinically relevant endpoints to evaluate drug effects?	6-MWT in PAH, MRI and multiple sclerosis
Identifiable target population (indication) that may benefit?	Biomarkers to identify responders and non-responders
What kind of comparison is useful, needed and feasible?	Placebo, active controls and dynamics in treatment options

Slide from presentation made by H. Leufkens in March 2010 at the:

REALIDADE NACIONAL NOS ENSAIOS CLÍNICOS?

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Challenges: Ongoing Commercial Clinical Trials – Bottom of Europe

Number of Existing Clinical Trials in Selected European Countries, per 5 Million Inhabitants

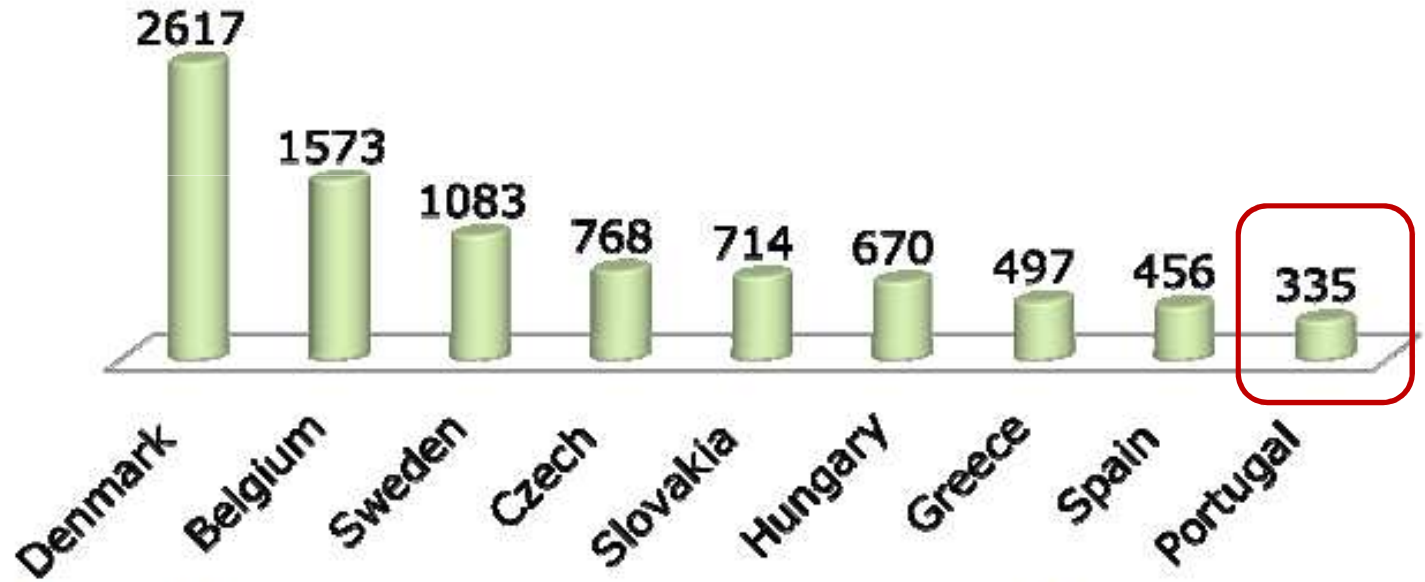

Chart created by P. Caetano using ClinicalTrials.gov; May 1, 2011

Source: Clinicaltrials.gov w/106,649 trials, 174 countries; Data confirmed also by 2 other sources: Newly created https://www.clinicaltrialsregister.eu/ and also LEEM 2010 report (1 trial per 100,000 in Port; 6 in Belg.)

Slide from presentation made by Pedro Caetano in May 2011 at the HMS

Number of New Trials in Portugal: Few (100+) & w/ Negative Growth

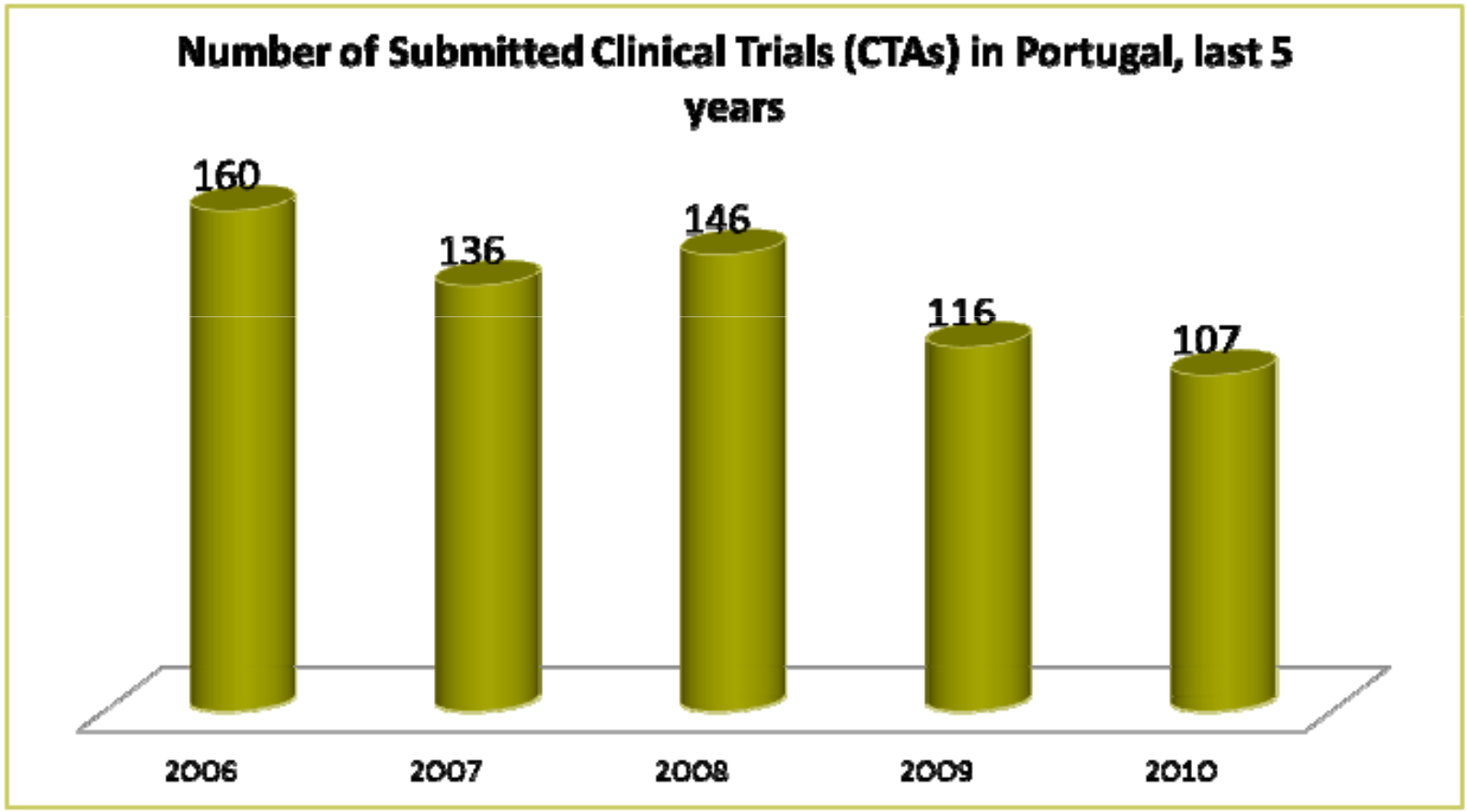

Chart created by P. Caetano using INFARMED data as of January, 2011

Slide from presentation made by Pedro Caetano in May 2011 at the HMS

DESENVOLVIMENTO DE FÁRMACOS EM PEDIATRIA

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Background

- 50%-75% dos medicamentos usados em Pediatria **não foram avaliados adequadamente** para este grupo etário.

- Desenvolvimento de Medicamentos em Pediatria **pouco apetecível para a Indústria Farmacêutica**:
  - População Pediátrica representa *apenas* 20% da população Europeia
  - Dificuldades Inerentes à realização de Ensaios Clínicos em Pediatria.

Acta Pediatr Port 2008; 39(1):17-22. Pharmacol Res. 2011 Sep;64(3):169-75.

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Background

- Elevada Prevalência da utilização de medicamentos *Não apropriados*:
  - Medicamentos sem AIM ou contra-indicados em crianças;
  - **Uso "Off-Label"**
    - Em relação à Faixa etária, Dose e Posologia, Via de Administração ou Indicação Terapêutica para uso em crianças
- Risco aumentado de ineficácia terapêutica ou RAM.

Acta Pediatr Port 2008; 39(1):17-22. Pharmacol Res. 2011 Sep;64(3):169-75.

BACKGROUND

- UTILIZAÇÃO BASEADA EM **EXTRAPOLAÇÕES DE DOSES** OU EM **MODIFICAÇÕES DE FORMULAÇÕES** PARA ADULTOS.
- POUCA INFORMAÇÃO SOBRE A SEGURANÇA E EFICÁCIA NESTA POPULAÇÃO.
- PRÁTICA CLÍNICA MUITO DEPENDENTE DA EXPERIÊNCIA ACUMULADA SOBRE DOSES, SEGURANÇA E EFICÁCIA.

Acta Pediatr Port 2008; 39(1):17-22. Pharmacol Res. 2011 Sep;64(3):169-75.

USO "OFF-LABEL" DE MEDICAMENTOS EM PEDIATRIA

- > EM UNIDADES DE CUIDADOS INTENSIVOS PEDIÁTRICOS E NEONATAIS E EM ONCOLOGIA COMPARATIVAMENTE AOS CUIDADOS PRIMÁRIOS;

- PRESCRIÇÕES DE MEDICAMENTOS *NÃO APROPRIADOS* ENVOLVIDAS EM RAM:

  23 A 60%

Expert Opin Drug Saf. 2006 Sep;5(5):703-18.

ORIGINAL ARTICLE

A prospective questionnaire assessment of attitudes and experiences of off label prescribing among hospital based paediatricians

J S McLay, M Tanaka, S Ekins-Daukes, P J Helms

Arch Dis Child 2006;**91**:584–587. doi: 10.1136/adc.2005.081828

What is already known on this topic:

- Paediatric off label prescribing is common in both primary and secondary care
- Off label prescribing is reportedly associated with increased levels of adverse drug reactions
- There is a European Union initiative to ensure appropriate assessment of all paediatric medicines

What this study adds:

- The majority of paediatricians have concerns about the safety and efficacy of off label medicines
- Paediatricians express the view that off label prescribing is associated with both adverse drug reactions and treatment failure in their patients
- A significant number of paediatricians expressed both concerns and less than wholehearted support towards the current EU drive to extend efficacy and safety data by promoting paediatric clinical trials

Many respondents did not believe it was necessary to carry out clinical trials in children for new (46%) or generic (64%) medicines. However, 52% of respondents stated that they would be willing to undertake clinical studies and recruit their own patients (61%) or children (73%) to take part in such studies.

British Journal of Clinical Pharmacology DOI:10.1111/j.1365-2125.2007.02865.x

Br J Clin Pharmacol | **64**:1 | 90–95 | 90

Attitudes and experiences of community pharmacists towards paediatric off-label prescribing: a prospective survey

Derek Stewart, Abdul Rouf, Ailsa Snaith, Kathleen Elliott, Peter J. Helms & James S. McLay

Department of Medicine and Therapeutics, University of Aberdeen, Aberdeen, UK

What is already known about this subject

- There are increasing concerns about the safety and efficacy of paediatric off-label medicines.
- In the UK, each year 26% of children receive an off-label prescription from their general practitioner.
- The community pharmacist is the final and key professional in the chain, with the responsibility to ensure that medicines are both prescribed and dispensed appropriately.

What this study adds

- The majority of community pharmacists are aware of off-label prescribing, but through work experience rather than undergraduate or postgraduate training or professional development.
- Community pharmacists, like UK general practitioners, underestimate the levels of paediatric off-label prescribing, and appear unclear as to the most common reasons for a prescription being off label.
- Most community pharmacists stated that they should inform the prescriber that a medicine was off label; however, when given specific practical examples, less than half would actually appear to do so.
- The majority of community pharmacists have been asked by the public to sell over-the-counter medicines for paediatric off-label use.

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Ensaios Clínicos em Crianças

Maria do Carmo Vale

Artigo 5º da Declaração de Helsínquia - *Medical progress is based on research that ultimately must include studies involving human subjects.*

Populations that are underrepresented in medical research should be provided appropriate access to participation in research [1].

Declaração de Helsínquia
59th WMA General Assembly,
Seoul, October 2008

I Jornadas

Comissão de Ética
para a Investigação Clínica

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ENSAIOS CLÍNICOS EM PEDIATRIA: PORQUÊ?

- NECESSIDADE DE CONHECER A **ESPECIFICIDADE DA PK E PD** DOS MEDICAMENTOS PEDIÁTRICOS.
- IMPORTÂNCIA DA **ESPECIFICIDADE DAS DOSAGENS** EM PEDIATRIA.
- EXISTÊNCIA DE DOENÇAS RARAS E RARÍSSIMAS EM CRIANÇAS.

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ENSAIOS CLÍNICOS EM PEDIATRIA – INVESTIGAÇÃO CLÍNICA

- IDENTIFICAR E PLANIFICAR OS DESAFIOS DA **PLANIFICAÇÃO E IMPLEMENTAÇÃO** DOS ENSAIOS PEDIÁTRICOS.
- RECONHECER A IMPORTÂNCIA DO **DESENHO ADEQUADO** AO OBJECTIVO ESPECÍFICO DO ENSAIO CLÍNICO.
- COMPREENDER AS **PREOCUPAÇÕES DOS PAIS DAS CRIANÇAS** ENVOLVIDAS EM INVESTIGAÇÃO.

CONSIDERAÇÕES ÉTICAS

- ADAPTAR DADOS OBTIDOS EM ENSAIOS COM POPULAÇÕES ADULTAS, PARA A CRIANÇA, **NÃO É CIENTÍFICO NEM ÉTICO**:
  - **CRIANÇAS NÃO SÃO PEQUENOS ADULTOS** E A POPULAÇÃO PEDIÁTRICA É MUITO HETEROGENIA;
  - PATOLOGIA INFANTIL DIFERE DA DOS ADULTOS E A **PK DE MUITOS MEDICAMENTOS VARIA COM A IDADE DA CRIANÇA**;
  - A TERAPÊUTICA ESPECIFICAMENTE DIRIGIDAS À POPULAÇÃO PEDIÁTRICA DEVE IR AO ENCONTRO DAS SUAS NECESSIDADES E **RECONHECER ESPECIFICIDADES**;

CONSIDERAÇÕES ÉTICAS

"A RESPONSABILIDADE DE PROTEGER A CRIANÇA DOS MALEFÍCIOS E EFEITOS ADVERSOS DOS ENSAIOS CLÍNICOS, NÃO SIGNIFICA PRIVÁ-LAS DOS SEUS BENEFÍCIOS, IMPEDINDO A SUA PARTICIPAÇÃO EM ENSAIOS QUE ABREM PERSPECTIVAS DE ACEDER A MEDICAMENTOS ESPECIFICAMENTE DESENVOLVIDOS PARA ELAS"

ENSAIOS CLÍNICOS EM POPULAÇÕES VULNERÁVEIS

Maria do Carmo Jardim Pereira do Vale – Membro da CEIC

REGULAÇÃO EUROPEIA

WHO International Clinical Trials Registry Platform

EU Paediatric Regulation

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Further information

European Medicines Agency
7 Westferry Circus
Canary Wharf
London E14 4HB
United Kingdom

Telephone +44 (0)20 7418 8400
Facsimile +44 (0)20 7418 8416
E-mail paediatrics@ema.europa.eu
Website www.ema.europa.eu

Resources on the Agency's website

Special topics > Medicines for children

Regulatory > Human medicines > Paediatric medicine

About us > Committees > PDCO

Partners & networks > Networks > Enpr-EMA

Better medicines for children

An agency of the European Union

EU PAEDIATRIC REGULATION

EC No. 1901/2006 (JANUARY 2007):

IMPROVE THE HEALTH OF CHILDREN IN THE EU BY:

- FACILITATING THE **DEVELOPMENT AND AVAILABILITY OF MEDICINES FOR CHILDREN** FROM BIRTH TO LESS THAN 18 YEARS.
- ENSURING THAT MEDICINES FOR USE IN CHILDREN ARE OF **HIGH QUALITY, ETHICALLY RESEARCHED**, AND AUTHORISED APPROPRIATELY.
- IMPROVING THE **AVAILABILITY OF INFORMATION** ON THE USE OF MEDICINES FOR CHILDREN.

http://www.ema.europa.eu/docs/en_GB/document_library/Other/2009/12/WC500026493.pdf

EU PAEDIATRIC REGULATION

EC No. 1901/2006 (JANUARY 2007):

IMPROVE THE HEALTH OF CHILDREN IN THE EU BY:

WITHOUT:

- SUBJECTING CHILDREN TO **UNNECESSARY TRIALS**, OR **DELAYING THE AUTHORISATION OF MEDICINAL PRODUCTS FOR USE IN ADULTS**.

http://www.ema.europa.eu/docs/en_GB/document_library/Other/2009/12/WC500026493.pdf

PAEDIATRIC INVESTIGATION PLANS (PIPS)

- ALL APPLICATIONS FOR MARKETING AUTHORISATION FOR NEW MEDICINES (NOT AUTHORISED IN THE EU BEFORE 26 JANUARY 2007) HAVE TO INCLUDE THE **RESULTS OF STUDIES CARRIED OUT IN CHILDREN OF DIFFERENT AGES**.
- ALSO APPLIES TO THE INTRODUCTION OF A NEW INDICATION, PHARMACEUTICAL FORM OR ROUTE OF ADMINISTRATION FOR A MEDICINE THAT IS ALREADY AUTHORISED AND PATENTED.

http://www.ema.europa.eu/ema/index.jsp?curl=pages/special_topics/general/general_content_000302.jsp&murl=menus/special_topics/special_topics.jsp&mid=WC0b01ac058002d4ea&jsenabled=true

PAEDIATRIC INVESTIGATION PLANS (PIPS)

- RESEARCH AND DEVELOPMENT PROGRAMME AIMED AT ENSURING THAT THE **NECESSARY DATA ARE GENERATED TO DETERMINE THE CONDITIONS IN WHICH A MEDICINAL PRODUCT MAY BE AUTHORISED FOR THE PAEDIATRIC POPULATION**.
- MUST SPECIFY THE TIMING AND THE MEASURES PROPOSED TO **ASSESS THE QUALITY, SAFETY AND EFFICACY OF THE MEDICINAL PRODUCT** IN ALL RELEVANT SUBSETS OF THE PAEDIATRIC POPULATION.
- MUST DESCRIBE ANY MEASURES TO **ADAPT THE FORMULATION OF THE MEDICINAL PRODUCT WHICH MAKE ITS USE MORE ACCEPTABLE, EASIER, SAFER OR MORE EFFECTIVE** FOR THE DIFFERENT SUBSETS OF THE PAEDIATRIC POPULATION

PDCO – PAEDIATRIC COMMITTEE

- EVALUATES PIPS HAVING IN CONSIDERATION:
  - STUDIES MUST BE DEVELOPED ONLY WHEN THERE IS AN EVENTUAL **THERAPEUTIC BENEFIT** FOR CHILDREN ARISING FROM THEM.
  - THE NEED FOR DEVELOPING CLINICAL STUDIES IN CHILDREN SHOULD NOT **DELAY THE AUTHORISATION OF MEDICINAL PRODUCTS FOR USE IN OTHER GROUPS OF PATIENTS**

http://www.ema.europa.eu/ema/index.jsp?curl=pages/special_topics/general/general_content_000302.jsp&murl=menus/special_topics/special_topics.jsp&mid=WC0b01ac058002d4ea&jsenabled=true

PDCO – PAEDIATRIC COMMITEE

- PDCO GRANTS:
  - **DEFERRALS**, ALLOWING A COMPANY TO DELAY DEVELOPMENT OF THE MEDICINE IN CHILDREN **UNTIL THERE IS ENOUGH INFORMATION TO DEMONSTRATE ITS EFFECTIVENESS AND SAFETY IN ADULTS**.
  - **WAIVERS** WHEN DEVELOPMENT OF A MEDICINE IN CHILDREN IS **NOT NEEDED OR IS NOT APPROPRIATE**, SUCH AS FOR DISEASES THAT ONLY AFFECT THE ELDERLY POPULATION.

http://www.ema.europa.eu/ema/index.jsp?curl=pages/special_topics/general/general_content_000302.jsp&murl=menus/special_topics/special_topics.jsp&mid=WC0b01ac058002d4ea&jsenabled=true

Rocchi *et al. Italian Journal of Pediatrics* 2010, **36**:56
http://www.ijponline.net/content/36/1/56

ITALIAN JOURNAL OF PEDIATRICS

DEBATE Open Access

The european paediatric legislation: benefits and perspectives

Francesca Rocchi[1*], Paolo Paolucci[2*], Adriana Ceci[3], Paolo Rossi[4]

Abstract

Background: The lack of availability of appropriate medicines for children is an extensive and well known problem. Paediatricians and Physicians who take care of the paediatric population are primarily exposed to cope with this negative situation very often as more than half of the children are prescribed off-label or unlicensed medicines.

Discussion: Medicinal products used to treat this population should be subjected to ethical research of high quality and be explicitly authorised for use in children as it happens in adults. For that reason, and following the US experience, the European Paediatric Regulation has been amended in January 2007 by the European Commission. The objective of the Paediatric Regulation is to improve the development of high quality and ethically researched medicines for children aged 0 to 17 years, to facilitate the availability of information on the use of medicines for children, without subjecting children to unnecessary trials, or delaying the authorisation of medicines for use in adults.

Summary: The Paediatric Regulation is dramatically changing the regulatory environment for paediatric medicines in Europe and is fuelling an increased number of clinical trials in the paediatric population. Nevertheless, there are some risks and pitfalls that need to be anticipated and controlled in order to ensure that children will ultimately benefit from this European initiative.

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RESPECT PROJECT

WWW.PATIENTNEEDS.EU

"*RELATING EXPECTATIONS AND NEEDS TO THE PARTICIPATION AND EMPOWERMENT OF CHILDREN IN CLINICAL TRIALS—RESPECT*" – GOALS:

- IDENTIFICATION CHILDREN'S NEEDS IN CLINICAL TRIALS FOR NEW MEDICINES;
- INCREASE EMPOWERMENT AND PARTNERSHIP OF FAMILIES IN CLINICAL TRIALS;
- DEFINE HOW CLOSER COLLABORATION OF ALL THE STAKEHOLDERS INVOLVED IN PAEDIATRIC CLINICAL TRIALS CAN FOSTER THE DEVELOPMENT OF MEDICINES THAT MATTER MOST TO CHILDREN.

(LAST MEETING: 25 MAY 2011, BRUSSELS)

IDEIAS-CHAVE

CHILDREN ARE NOT SIMPLY YOUNG ADULTS

- MEDICAMENTOS DE USO PEDIÁTRICO COM **AIM ESPECÍFICA**
- **INCENTIVOS E APOIOS** À INVESTIGAÇÃO CLÍNICA EM PEDIATRIA
- NÃO EXPOR DESNECESSARIAMENTE CRIANÇAS A ENSAIOS CLÍNICOS
- **MELHORAR INFORMAÇÃO** DISPONÍVEL PARA A UTILIZAÇÃO DE MEDICAMENTOS PEDIÁTRICOS

WEBSITES A CONSULTAR

- MAKE MEDICINES CHILD SIZE (WHO)

  HTTP://WWW.WHO.INT/CHILDMEDICINES/EN/INDEX.HTML

- INTERNATIONAL CLINICAL TRIALS REGISTRY PLATFORM (ICTRP)

  HTTP://WWW.WHO.INT/ICTRP/EN/

- MEDICINES AND HEALTHCARE PRODUCTS REGULATORY AGENCY (MHRA) - UK

  HTTP://WWW.MHRA.GOV.UK/HOWWEREGULATE/MEDICINES/MEDICINESFORCHILDREN/INDEX.HTM#L5

- STAR CHILD HEALTH – INTERNATIONAL FORUM OF STANDARDS FOR RESEARCH IN CHILDREN HTTP://WWW.STARCHILDHEALTH.ORG

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WEBSITES A CONSULTAR

- EUROPEAN MEDICINES AGENCY (EMA) - MEDICINES FOR CHILDREN

  HTTP://WWW.EMA.EUROPA.EU/EMA/INDEX.JSP?CURL=PAGES/SPECIAL_TOPICS/GENERAL/GENERAL_CONTENT_000302.JSP&MURL=MENUS/SPECIAL_TOPICS/SPECIAL_TOPICS.JSP&MID=WC0B01AC058002D4EA&JSENABLED=TRUE

- EUROPEAN NETWORK OF PAEDIATRIC RESEARCH AT THE EUROPEAN MEDICINES AGENCY (ENPR-EMA)

  HTTP://WWW.EMA.EUROPA.EU/EMA/INDEX.JSP?CURL=PAGES/PARTNERS_AND_NETWORKS/GENERAL/GENERAL_CONTENT_000303.JSP&MURL=MENUS/PARTNERS_AND_NETWORKS/PARTNERS_AND_NETWORKS.JSP&MID=WC0B01AC05801DF74A

OBRIGADO PELA ATENÇÃO!

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