Safeguarding public health

Medicines for children

Regulation on medicines for paediatric use EC No 1901/2006

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DGRA conference
June 2007

Key elements for discussion

European Paediatric Committee (PDCO)

Paediatric Investigation Plan (PIP)
- modifications, deferrals, waivers, compliance checks

Requirements
- requirement for paediatric data based on PIP
- submission of existing data
- pharmacovigilance

Incentives
- 6 months extension SPC
- 2 years extension market exclusivity
- data and market protection

Paediatric use marketing authorisation (PUMA)

Publicly accessible paediatric clinical trials database

European network

Paediatric study program

Decision making process

Identification

Paediatric Committee

New scientific committee established in EMEA

Expertise in areas relevant to paediatric medicine

Member States : 22
CHMP : 5
Stake-holders : 3+3
Operational with 27 members

Plus alternates

Tasks related to objectives

“Established” by July 2007

Tasks of Paediatric Committee

- Opinions
  - PIP
  - Waiver
  - Deferral
  - Compliance (on request)
  - Safety, efficacy, quality of data from PIP (on request)

Agency decision

- Inventory of therapeutic needs
- Advice on EU paediatric clinical trials network
- Identification (explained in PIL)

Taking into account significant therapeutic benefit or therapeutic need

Requirements

"An application for MA under Article 6 of Directive 2001/83/E in respect of a medicinal product for human use which is not authorised in the Community at the time of entry into force of this Regulation shall be regarded *as 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*
- *decision* of the Agency granting a *product-specific waiver*
- *decision* of Agency granting a *class waiver*
- *decision* of Agency granting a *deferral*

Requirements

Enters into force 26 July 2008

Requirements

Also applies to *authorised* MPs protected by *SPC or qualifying patent*

- If applying for *new indications*, *new pharmaceutical forms* and *new routes of administration*
- PIP must cover both *existing and new* indications, pharmaceutical forms and routes of administration

Enters into force 26 January 2009

NB Does not apply if no longer covered by SPC or patent

Requirements

Not *generic, well-established use, homeopathic or herbal* products

Not to delay MA in *adults*

- *deferrals*

No *unnecessary* clinical or other *trials* in paediatric population

- *waivers*

Deferrals

- Deferral ≠ deferral of requirement ≠ no need for PIP
- Deferral refers to *timing* of *initiation or completion* of *some or all* studies and measures *in relation to initial MAA*
- Application for deferral *at time of first submission of PIP*
- Justified on grounds of:
  - *scientific/technical issues*
  - *public health*
- May be *imposed* by PDCO
- Regular checks / annual report – update on progress

Waivers

No requirement for PIP if evidence showing:

- MP likely to be ineffective or unsafe
- Disease/condition *confined to adults*
- *No significant therapeutic benefit* over existing treatments for paediatric patients

Waivers

- Class
- Product specific

- Requested
- Imposed

- Partial
- Full

- Indication(s)
- Subset(s)
  - all or part of paediatric population

Waivers

Must always apply for a waiver even if class waiver applies

Decision must be included for validation of MAA

Waivers

Procedure

- Apply at end of phase I adults
- Rapporteur
- 60 days to opinion
- RSI (suspend timetable)
- Meet rapporteur/PC

Waivers

- List of all waivers published
- Waivers can be reviewed and revoked
- If revoked, requirement for PIP applies 36 months after date of removal from list

Decision making process

EMEA not Commission
All decisions published

Opinion ____ 10 days ____ Applicant

Applicant ____ 30 days ____ Re-examination request

Request ____ 30 days ____ New rapporteur & new opinion

New opinion ____ 10 days ____ Decision

Appeal to ECJ

Compliance

Verified by competent authority/EMEA (validation)

RMS responsibility if MRP/decentralised

PDCO may be consulted for opinion by:

- applicant (presubmission)
- EMEA/national c.a. (validation)
- CHMP/national c.a. (during assessment)

Statement of compliance in MA

Important - no incentives if no statement (non-compliant)
ie no SPC extension (Art 36) for MPs
no ME extension (Art 37) for OMPs
no data & market protection (Art 38) for PUMAs .

(Commission guideline)

Paediatric investigation plan

- " research and development programme aimed at ensuring that the necessary data are generated determining the conditions in which a medicinal product may be authorised to treat the paediatric population"

  - *timing and measures*
  - *all relevant age groups and formulations*
  - *including "non-adult" indications*

- free scientific advice

- ≠ FDA written request

Paediatric investigation plan

- Submitted to PDCO prior to submission of MAA (unless waiver)
  - end phase I adults (preliminary)

- PDCO
  - considers study methodology and expected therapeutic benefit
  - may request modifications
  - may grant waiver or deferral (partial)
  - gives positive or negative opinion (waiver)

- 90 day time frame
  - 30 d validation and SR
  - 60d to appoint rapporteur and adopt opinion
  - Clock stop(s) for RSI(s)
  - Meetings with rapp/PDCO

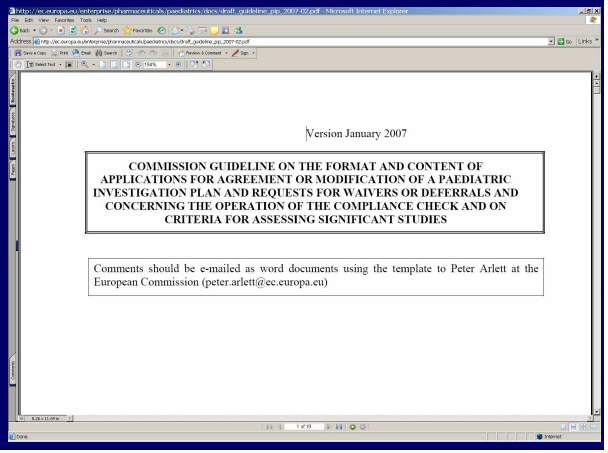
- 1 opportunity for re-evaluation of opinion (new Rapporteur 30d) .

Agreed Paediatric Investigation Plan

- opinion → EMEA Decision (published)
- serves as basis for evaluation of the MA application
- must be completed
  - timing depends on deferrals
  - modifications if difficulties encountered .

Paediatric investigation plan

- Commission guideline on format and contents of PIP (also compliance check and significant studies)
- Released for consultation 29 January 2007
  - http://ec.europa.eu/enterprise/pharmaceuticals/paediatrics/docs/draft_guideline_pip_2007-02.pdf
- Comments 30 March 2007 .


Version January 2007

COMMISSION GUIDELINE ON THE FORMAT AND CONTENT OF APPLICATIONS FOR AGREEMENT OR MODIFICATION OF A PAEDIATRIC INVESTIGATION PLAN AND REQUESTS FOR WAIVERS OR DEFERRALS AND CONCERNING THE OPERATION OF THE COMPLIANCE CHECK AND ON CRITERIA FOR ASSESSING SIGNIFICANT STUDIES

Comments should be e-mailed as word documents using the template to Peter Arlett at the European Commission (peter.arlett@ec.europa.eu)

Commission guideline

Section 1 Draft format and contents
Agreement, modification, waivers, deferrals

General

- all subsets of the paediatric population
- age-appropriate formulations
- therapeutic benefit +/or need

Specific

NB detailed

- A Administrative and product information
- B Overall MP development
- C Product specific waivers
- D Paediatric Investigation Plan

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D Paediatric Investigation Plan

D1 Overall strategy for paediatric development

D2 Strategy in relation to quality

D3 Strategy in relation to non-clinical

D4 Strategy in relation to clinical

D5 Planned measures

- Overall summary table of all studies
- Outline each planned/performed study/step in pharm dev
- Protocol synopsis each planned/performed study
  - non-clinical
  - clinical

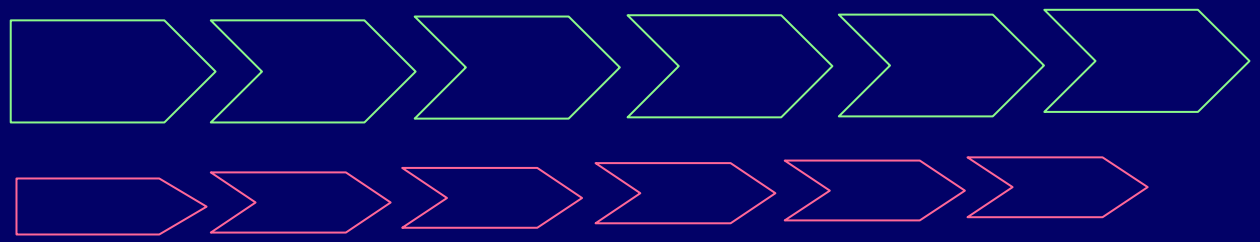
D Paediatric Investigation Plan
Protocol synopsis for clinical study

- Type of study
- Study design
- Type of control (placebo or active control with dose to be used)
- Location (regions)
- Test(s) products; Dosage regimen; Route of administration
- Objective(s) of the study
- Number of subjects (M/F), ages, number per ICH age groups or other relevant age group
- Duration of treatment
- Main inclusion/ exclusion criteria
- Parameters or endpoints (primary, secondary)
- Sample size (more or less detailed as appropriate)
- Power calculation: describe effect size expected
- Options in case of recruitment issues, interim analyses and stopping rules
- Statistical methods (Statistical methods used to compare groups for primary outcome, and for additional analyses if relevant)

D Paediatric Investigation Plan

D6 Timelines of measures

- timing in relation to studies in adults
- predicted timing in relation to submission of MAA (Arts 7&8)
- timelines for initiation and completion (specific dates)
- include timelines for analysis and reporting .



E Deferrals

Deferral of initiation or completion of studies

- justified by indication, route, form
- specify age group
- justifications
  - scientific/technical
  - public health

Examples

- appropriate to conduct studies in adults prior to initiating studies in paediatric population
- studies in paediatric population longer to conduct than studies in adults
- additional non-clinical data necessary
- major quality problems prevent development of relevant formulation(s)

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F Annexes

- References
- IB
- Opinions and decisions of CAs including 3rd countries
- Scientific advice given by CAs including 3rd countries
- Latest approved product information, if already authorised .

Draft guideline on PIP, compliance and significant studies

Section 2 Compliance check

No renegotiation of measures and timelines (modifications)

Full study reports

Not a safety and efficacy assessment

Section 3 Assessment criteria for significance of studies

Quality not quantity

Clinical relevance for paediatric indication

Completion = last visit of last patient as foreseen in protocol

Examples

- Comparative efficacy studies (randomised controlled)
- Dose-finding studies
- Prospective clinical safety studies, if major contribution from results to safe use in paediatric population
- Studies for new age-appropriate formulation, if clinically relevant .

Incentives

Medicinal Products (Article 36)

- 6 months extension of duration of period of SPC

Conditions

- active SPC
- certified completed compliant agreed PIP
- information from PIP in SmPC
- MP authorised in all MSs (cf. marketed)
- must apply for extension not later than 2 yrs before expiry of SPC (6mo until January 2012)
- "Significant" studies in PIP must be completed after Regulation enters into force

NB ❖ incentive not dependent on paediatric indication

❖ imposed waiver denies incentives .

Incentives

Orphan medicinal products (Article 38)

- 2 years additional market exclusivity

Conditions

- certified completed compliant agreed PIP
- information from PIP in SmPC
- MP authorised in all MSs (already condition of ME)
- "Significant" studies in PIP must be completed after

Regulation enters into force

NB incentive not dependent on paediatric indication
imposed waiver denies incentives

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Paediatric Use marketing authorisation (PUMA)

Requirements

- off-patent
- agreed PIP
- “significant” studies in PIP must be completed after Regulation enters into force

Incentives

- eligible for centralised procedure – reduced fee
- can refer to dossiers of same active (even if not MAH)
- can keep same brand name (if MAH)
- data (8 y) and market (10y) protection (+1)
  - covers paediatric studies only
- 26 July 2007 .

Paediatric Use marketing authorisation (PUMA)

Legal basis of applications

Could be based on:

- Article 8 (3)
- Article 10(3)
- Article 10(4)
- Article 10b

Inappropriate:

- Article 10 (1) (generics)
- Article 10 a (well-established use)
- Article 10 c (informed consent)

If off-patent
and developing
- new paediatric indication/dose/strength

and not applying for a PUMA

There is no requirement for an agreed PIP

Paediatric study programme

- for off-patent medicines or active substances

- Community framework programmes
  - call for proposals (second) FP7-HEALTH-2007-A
  - adapting off-patent medicines to the specific needs of paediatric populations.
    - deadline 18 September 2007
    - phase I-IV
    - aiming at PUMA
    - evaluation based on priority list

  - expect to fund several projects .

Adapting off-patent medicines to the specific needs of paediatric populations

Support will be given to studies dedicated to provide evidence for specific paediatric use of off-patent medicinal products currently used off-label. Studies include the assessment of pharmacokinetics (as well as data analysis and extrapolation by means of *in silico* models), efficacy and safety, and/or the development of appropriate formulations.
Project proposals must take account of the priority list of Off-Patent Medicinal Products of the Paediatric Working Party of the European Medicines Agency (EMEA), and of the Regulation of the European Parliament and of the Council on medicinal products for paediatric use and amending Regulation (EEC) N°1768/92, Directive 200 1/83/EC and Regulation (EC) N° 726/2004, Brussels, 29.9.2004, COM(2004) 599 final, 2004/0217 (COD).
The priority list is available at the following address:
http://www.emea.europa.eu/pdfs/human/peg/49677706en.pdf

Funding scheme:
Collaborative projects (Small or medium-scale focused research projects with a maximum EC contribution of € 6,000,000/project).

Expected Impact: The projects will provide evidence for a better use of off-patent medicinal products in paediatric populations. The acquired knowledge should aim at eventual new Paediatric Use marketing authorisations (PUMAs).

http://cordis.europa.eu/fp7/dc/index.cfm?fuseaction=UserSite.CooperationDetailsCallPage&call_id=10 .

European Network

- network of :
  - national and European networks
  - investigators
  - centres

- objectives include:
  - facilitate high quality, safe & ethical studies
  - ensure effective coordination & communication
  - stimulate harmonisation of procedures & quality standards
  - stimulate & facilitate new networks and centres
  - ensure compatibility with Community framework programmes
  - avoiding unnecessary duplication

- EMEA → implementing strategy by 26 January 2008.

European Network

NB

- no dedicated funds
- no interference with integrity of national networks

National networks

- Some already up and running eg UK MCRN
- others being planned

Strengthened paediatric pharmacovigilance
New requirements

- MAH to give additional measures to ensure follow-up of efficacy and possible ADRs to an authorised paediatric use
- risk management system or specific post-marketing studies required, as a condition of MA, if particular cause for concern
- MAH to assess RMS and results of any pm studies and include in PSURs
  - can also request additional assessments
- CHMP guideline on paediatric PV – entered into force same date as Regulation.

Paediatric clinical trials database

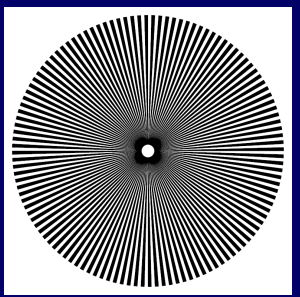
- EUDRACT database
- includes trials conducted solely in 3rd countries
- elements, including results, to be publicly available
  - based on CONSORT*
  - fairly detailed
  - results public whether or not premature termination
  - ? timing

- consultation on guidance

*consolidated standards of reporting trials

Identification

- Symbol – likely to be very abstract
- Package label all MPs with paediatric indication
- Retrospective ie products authorised pre-Regulation
  - (2 years)
- Industry consultation
- Adopted by Commission, advised by PDCO
- Explanation in PIL



Use of Community procedures

Existing non-centrally authorised products
AND
Extension of use in the paediatric population

- indication
- pharmaceutical form
- route of administration

Can submit application under Arts 32, 33, 34 of 2001/83/EC

Procedure limited to specific sections of the SmPC

Results in harmonised paediatric information for unharmonised MPs

Discontinuation

IF MP has

- paediatric indication
- benefited from SPC extension (Art 36)
  ME extension (Art 37)
  data/market protection (Art 38)

AND above periods expired

then IF intend to discontinue

Must transfer MA or allow 3rd party to use documentation
Must inform EMEA of intention to d/c 6 months beforehand
EMEA must publish names of MAH and MP.

Fees

FREE

- Waiver
- Deferrals
- PIPS
- Compliance check (PDCO)
- Scientific advice

REDUCED FEE

- PUMA (centralised)

Penalties

Infringements of Regulation or implementing measures

- National
  - effective, proportionate, dissuasive
  - inform Commission
- Commission
  - financial penalties
  - publish names of anyone infringing + details financial penalties

Other elements

Submission of data (Article 45)

- all existing completed* studies to be submitted by 26 January 2008
- CAs may vary MA as appropriate
- eligible for inclusion in PIP
- Commission guideline - assessment criteria for significant studies
- No need to resubmit data already submitted

*by date of entry into force of 1901/2006

Progress on Implementation

1st meeting PDCO July 2007

Commission guideline released 29 January 2007

- PIP
- compliance check
- significant studies

Call for proposals issued deadline 18 September 2007

Other drafts in development on

- research network
- database
- symbol
- submission of data