5 October 2012
EMA/PDCO/565104/2012
Human Medicines Development and Evaluation

Paediatric Committee (PDCO)

Final minutes of the 05-07 September meeting

Chair: Daniel Brasseur

I Introduction

I.1 Adoption of the minutes from previous meeting

Adopted.

http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/document_listing/document_listing_000192.jsp&mid=WC0b01ac0580028eab

I.2 Adoption of the Agenda

Adopted with modifications.

http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/document_listing/document_listing_000192.jsp&mid=WC0b01ac0580028eab

I.3 Declaration of Conflict of Interest

See Annex I.

I.4 External attendance

Please refer to the September 2012 PDCO monthly report published in the EMA Website:

http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/document_listing/document_listing_000192.jsp&mid=WC0b01ac0580028eab

I.5 Leaving/New Members and Alternates

Please refer to the September 2012 PDCO monthly report published in the EMA Website:

http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/document_listing/document_listing_000192.jsp&mid=WC0b01ac0580028eab

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II Opinions

II.1 Opinions on Products

II.2 Opinions on Compliance Check

II.3 Opinions on Modification of an Agreed Paediatric Investigation Plan

Please refer to the September 2012 PDCO monthly report published in the EMA Website:

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III Discussion of applications

The PDCO discussed 84 procedures in total[1], of which:

- 34 paediatric investigation plan applications;
- 17 product-specific waiver applications;
- 3 compliance check procedures (interim and final);
- 29 requests for modifications of an agreed paediatric investigation plan.
- 1 re-examination request.

IV Nomination of Rapporteurs and Peer reviewers

• List of letters of intent received for submission of applications with start of procedure November 2012[1] for Nomination of Rapporteur and Peer reviewer • Nomination of Rapporteur for requests of confirmation on the applicability of the EMA decision on class waiver	The PDCO approved the lists of Rapporteurs and Peer Reviewers.

V Update and finalisation of opinions and requests for modification

All opinions taken at this meeting (relating to adoption of opinions, recommendations, requests for modifications and applicability of class waivers) were made in the presence of the required quorum of members.

The opinions adopted during the Paediatric Committee meeting of September are published in the same month's meeting report published in the EMA website: http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/document_listing/document_listing_000192.jsp&mid=WC0b01ac0580028eab.

[1] The procedures discussed by the PDCO are on-going and therefore are considered confidential. Additional details on these procedures will be disclosed in the PDCO Committee meeting reports (after the PDCO Opinion is adopted), and on the Opinions and decisions on paediatric investigation plans webpage (after the EMA Decision is issued).

VI DISCUSSION OF THE APPLICABILITY OF CLASS WAIVER

Class waiver number	Active substance	Condition	Outcome (confirmed / not confirmed)
EMEA-37-2012	BI 836845	Treatment of lung carcinoma (small cell and non-small cell carcinoma)	Confirmed
EMEA-38-2012		Treatment of liver and intrahepatic bile duct carcinoma (excluding hepatoblastoma)	Confirmed
EMEA-39-2012		Treatment of breast carcinoma	Confirmed
EMEA-40-2012		Treatment of prostate carcinoma (excluding rhabdomyosarcoma)	Confirmed
EMEA-41-2012	Lisuride Hydrogenmaleate (LHM)	Treatment of Parkinson's disease (non juvenile)	Confirmed
EMEA-42-2012	MEHD7945A	Adenocarcinoma of the colon and rectum	Confirmed
EMEA-43-2012		Oropharyngeal, laryngeal or nasal epithelial carcinoma (excluding nasopharyngeal carcinoma or lymphoepithelioma)	Confirmed
EMEA-44-2012	Nicotinic Acid / Laropiprant	Treatment of coronary atherosclerosis	Postponed to October
EMEA-45-2012	Perindopril tosilate/Amlodpine besilate	Treatment of coronary atherosclerosis	Confirmed

VII Other topics

Guidelines	
Advice to EC on revised 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	The PDCO discussed the draft new guideline. Several suggestion were offered, including : • Addition of "contraception" as an example of possible condition in the definitions; • A clear distinction of the use of the word "condition", when it means "medical condition in a PIP" rather than the more common use of the word ("situation"). • Clarification that applicants are not requested to propose several alternative developments, for the PDCO to choose, but rather to justify their proposal. • Highlighting the difference of detail level between the application and the opinion.

	• Addition of the possibility to request a presubmission meeting. • More detailed definition of potential grounds for "lack of significant benefit" (e.g. when studies are unfeasible, or trials are not expected to provide significant benefit for children). • More consistent use of "key elements" rather than "measures", when applicable. • Better clarification on the possibility of proposing extrapolation, and the relevant justifications. • Deletion of all numbering of headings and subheadings from guideline. The document will be edited and re-sent to the PDCO for further discussion in October, and possible adoption in November.
Concept paper on the involvement of Children and Young People	The PDCO were informed that no further comments had been received on the proposed Concept Paper. Therefore, the Concept Paper was adopted for a two month public consultation period, starting 17 September 2012. All Member States are actively encouraged to seek relevant bodies to contribute during this time.
Guideline on the clinical development of medicinal products intended for the treatment of chronic primary immune thrombocytopenia*	PDCO was involved in the drafting of the Concept Paper, however not part of the drafting group for the guideline. Either PDCO will provide comments within one month on the existing document circulated, or if the paediatric development is considered to be very different from that in adults, a paediatric addendum will be considered.
Working groups	
Breakout group for the revision of the standard allergen PIP	Postponed to October
Breakout group for the revision of the standard asthma PIP	The ad-hoc group of PDCO members agreed to not develop a detailed standard asthma PIP, but to define a development strategy in line with the recommendations currently discussed for the revised EMA asthma guideline which will contain a dedicated and detailed chapter for children which has been discussed by PDCO. The draft strategy will be presented to PDCO plenary at next month meeting.
Paediatric Inventory working group	The discussion on the current therapeutic area (infectious diseases) was briefly reported to the PDCO.
Paediatric oncology working group	A brief discussion of product-related issues and non-product related issues, the latter including model oncology PIPs, coordination of participation in external meetings,

	preparation of paediatric oncology task force meeting, data for response letter to paediatric neuro-oncologists was reported to PDCO.
Formulation working group	No non-product related issues where reported to the Committee
Non-Clinical working group	No non-product related issues where reported to the Committee
Extrapolation working group	It is agreed that the Extrapolation group will start from October onwards with the drafting of the extrapolation reflection paper. However the scope of the reflection paper will be more paediatric orientated than the concept paper. External comments on the Concept Paper are expected for end of September and will be incorporated in the drafting of the Reflection Paper.
Other topics	
Brief report on the workshop on clinical development and scientific advice in ophthalmology	The PDCO was updated on the outcomes of the workshop on ophthalmology, the main issues having been Paediatric Investigation Plans for uveitis, glaucoma, keratoconjunctivitis, limbal stem cell deficiency and retinopathy of the premature.
Validation of marketing authorisation / variation / line extensions applications when the PIP / waiver was granted to a different applicant	The PDCO was informed that the Paediatric Regulation does not require that the applicant for marketing authorisation (or another regulatory procedure) is the same as the PIP (or waiver) addressee, and there is no official procedure to "transfer" a PIP or waiver to a different company or person (contrary, for example, to orphan drug designations). However, the legislation does require that applicants for marketing authorisation have an agreed PIP or waiver; this can be ensured by requesting applicants for regulatory procedures to attach the full EMA decision on the PIP/waiver, i.e. the document that contains decision, opinion and summary report in a single (PDF) file. The EMA however encourages applicants to inform the Agency, using the specific template, when development of a product is transferred to another entity, to update the data of the contact person for interested parties on the website. The Paediatric subgroup of the CMDh has also been informed.

VIII Any other business

- **Review of the EMA decision on the list of class waivers:**

  The PDCO had a preliminary discussion on the possibility of revoking the existing class waivers that are aimed at a condition, rather than at a specific class of medicinal products (in a given

condition). Experience so far has suggested that, particularly for products in the therapeutic area of oncology, the existence of the class waivers has been detrimental to paediatric needs insofar as it often prevents the agreement on PIPs for products with relevant (and broad) mechanisms of action, potentially of interest in paediatric cancers. A draft document* on the potential justifications for a revoke of the class waivers has been prepared by the EMA Secretariat, and distributed in July to PDCO members; it will form the basis for the discussion and potential approval of a PDCO opinion in the following months.

- **EMA/FDA Workshop for Paediatric Gaucher disease Type I - exploring the way forward**:

  The PDCO were informed that a joint workshop of the EMA and FDA is to be held 17-18 Sept 2012 – inviting industry, experts and patient representatives. All PDCO members invited to participate too.

- **Draft Guideline on clinical investigation of medicinal products in the treatment of schizophrenia**:

  The PDCO discussed the draft new guideline, and the differing views on the need for long-term efficacy data, versus the possibility of accepting extrapolation from data in adults for long-term efficacy in children and adolescents, based on short-term PK and efficacy data in paediatric age groups.

  The PDCO has so far requested maintenance of efficacy studies in all PIPs for products intended to treat schizophrenia, with the intent of collecting evidence to support future extrapolation of maintenance of efficacy from adults to adolescents. The severity and the course of the disease appear to be different in children from adults. No data are available differences in pharmacology of antipsychotic medicines between adults and children but differences exist due to brain maturation; furthermore, while the disease may be considered similar, it may have different causes or aggravating factors such as illicit drug use.

  The PDCO heard that FDA have agreed to extrapolation on the basis of alleged lack of feasibility of placebo-controlled studies. In fact several long-term efficacy studies included in approved PIPs are ongoing or planned (not necessarily placebo-controlled) although they are clearly challenging.

  The PDCO therefore considers that, at present, generation of evidence of long term efficacy data is necessary for evidence based decisions and extrapolation of long-term efficacy in paediatric age groups is not based on sufficient evidence. The PDCO is of the view that the guideline should consider extrapolation as acceptable only once sufficient supporting evidence has been generated.

  The co-operation with all involved parties to finalise the Guideline is continuing.

- **General report on experience acquired as a result of the application of the paediatric regulation** (Article 50(3) of Regulation (EC) no 1901/2006)

  The Agency received, during the PDCO meeting, the draft Consultation paper♦, prepared by the European Commission with a view to set out a public consultation to obtain input from stakeholders, especially industry but also patient and healthcare representatives, on their experience with the paediatric regulation. The document, containing 11 statements on which input will be sought by the EC, was briefly presented to the PDCO. *(Post meeting note: the document is now published on the EC website)*

♦ Post meeting note: The General reports was published on the European Commission website on 19 September 2012.

- **Corrigenda**

  In connection with a PIP procedure, the PDCO discussed the use of a specific rating scale for the collection of adverse events and established that it is not in the public domain yet. The scale in question, however, has been included as key element in two other PIP Decisions over the past months.

  The PDCO therefore adopted two Corrigenda, to remove the requirement to use this specific scale.

Note on access to documents

Documents marked with an asterisk* in these minutes cannot be released at present as they are currently in draft format. They will become public when adopted in their final form.

Annex I to the Minutes of the PDCO of September 2012

Documentation on Declaration of interest of members, alternates and experts

Based on the Declarations of interest submitted by the Committee members, alternates and experts and based on the topics in the agenda of the current meeting, the Committee Secretariat announced the restricted involvement of Committee members for the upcoming discussions.

In accordance with the Agency's revised Policy and Procedure on the handling of conflicts of interests, participants in this meeting were asked to declare any conflict of interests on the matters for discussion (in particular any changes, omissions or errors to the already declared interests).

Member, alternate, expert name	Outcome restriction following evaluation of electronic Declaration of Interests	Topics on the current Committee Agenda for which this restriction applies
Adriana Ceci	Restriction level 3	EMEA-C2-000548-PIP01-09-M03
Adriana Ceci	Restriction level 3	EMEA-000366-PIP01-08-M05
Adriana Ceci	Restriction level 3	EMEA-001322-PIP01-12
Adriana Ceci	Restriction level 3	EMEA-001321-PIP01-12
Adriana Ceci	Restriction level 3	EMEA-001315-PIP01-12
Adriana Ceci	Restriction level 3	EMEA-001258-PIP01-11
Adriana Ceci	Restriction level 3	EMEA-001196-PIP01-11
Adriana Ceci	Restriction level 3	EMEA-001071-PIP02-12
Alexandra Compagnucci	Restriction level 3	EMEA-C1-001181-PIP01-11
Carine de Beaufort	Restriction level XR	EMEA-001178-PIP01-11
Dobrin Konstantinov	Restriction level 3	EMEA-001301-PIP01-12
Dobrin Konstantinov	Restriction level 3	EMEA-001301-PIP02-12
Gerard Pons	Restriction level 3	EMEA-001258-PIP01-11
Igor Francetic	Restriction level DP	EMEA-000439-PIP02-11
Marek Migdal	Restriction level 4	EMEA-001211-PIP01-11
Marek Migdal	Restriction level 4	EMEA-000205-PIP02-11
Matthias Keller	Restriction level 4	EMEA-001305-PIP01-12
Matthias Keller	Restriction level 4	EMEA-001302-PIP01-12
Michal Odermarsky	Restriction level XP	EMEA-001307-PIP01-12
Michal Odermarsky	Restriction level XP	EMEA-001219-PIP01-11

Member, alternate, expert name	Outcome restriction following evaluation of electronic Declaration of Interests	Topics on the current Committee Agenda for which this restriction applies
Kolbeinn Gudmundsson	Restriction level DP	Confirmation of applicability of class waiver EMEA-45-2012
Kolbeinn Gudmundsson	Restriction level DP	Confirmation of applicability of class waiver EMEA-44-2012

Note: the procedures identified in the table above are on-going and therefore considered commercially confidential. Additional details on these procedures will be disclosed in the PDCO Committee meeting reports (after the PDCO Opinion is adopted), and on the Opinions and decisions on paediatric investigation plans webpage (after the EMA Decision is issued).

No new or additional conflicts were declared.

Discussions, deliberations and voting took place in full respect of the restricted involvement of Scientific Committee members and, where relevant, experts attending the plenary meeting, as announced by the Scientific Committee Secretariat at the start of meeting.

Restriction levels:

The European Medicines Agency recently reviewed and updated the coding used in the evaluation of the conflict of interest. There will be a short transition period when both codes will be in used until procedures evaluated under the previous code have been completed.

Evaluation of the conflict of interest – Previous code	
Outcome	Impact
1	No involvement in activity
2	To be replaced for the discussions, final deliberations and voting as appropriate in relation to the relevant product or a competitor product.
3	Where Individual product involvement is declared: - No involvement with respect to procedures involving the relevant product or a competitor product in the relevant indication, i.e. no part in discussions, final deliberations and voting as appropriate as regards these medicinal products.
4	Where Individual product involvement is declared: - Involvement in discussions only with respect to procedures involving the relevant product or a competitor product, i.e. no part in final deliberations and voting as appropriate as regards these medicinal product.

Evaluation of the conflict of interest – New code	
Outcome	Impact
R-P	To be replaced for the discussions, final deliberations and voting as appropriate in relation to the relevant product or a competitor product.
XP	Where Individual product involvement is declared - PRODUCT INDICATION: - No involvement with respect to procedures involving the relevant product or a

Evaluation of the conflict of interest – New code	
	competitor product in the relevant indication i.e. no part in discussions, final deliberations and voting as appropriate as regards these medicinal products. - Cannot act as Rapporteur for these products - [Cannot act as Rapporteur for development of guidelines in concerned therapeutic area].
XC	Where cross product / general involvement is declared - COMPANY: - No involvement (as outlined above) with respect to products from the specified company. - Cannot act as Rapporteur for products from the relevant company(ies).
DP	Where Individual product involvement is declared - PRODUCT INDICATION: - Involvement in discussions only with respect to procedures involving the relevant product or a competitor product i.e. no part in final deliberations and voting as appropriate as regards these medicinal products. - Cannot act as Rapporteur for these products.
DC	Where cross product / general involvement is declared - COMPANY: - Involvement in discussions only with respect to products from the specified company. - Cannot act as Rapporteur on products from the relevant company(ies).
XR	Committee member cannot act as Rapporteur or Peer reviewer in relation to any medicinal product from the relevant company.
R-C	To be replaced for the discussions, final deliberations and voting as appropriate in relation to any medicinal product from the relevant company

Annex II to the Minutes of the PDCO of September 2012

List of Participants

Chair

Daniel BRASSEUR

Vice-chair

Dirk MENTZER

Members appointed by Member States or CHMP

Christoph MALE	Austria
Koenraad NORGA	Belgium
Dobrin KONSTANTINOV	Bulgaria
Marianne ORHOLM	Denmark
Pirjo LAITINEN-PARKONNEN	Finland
Gerard PONS	France
Dirk MENTZER	Germany
Stefanos MANTAGOS	Greece
Agnes GYURASICS	Hungary
Gylfi OSKARSSON	Iceland
Kevin CONNOLLY	Ireland
Paolo ROSSI	Italy
Dina APELE-FREMIANE	Latvia
Carine de BEAUFORT	Luxembourg
Hendrik van den BERG	The Netherlands
Siri WANG	Norway
Marek MIGDAL	Poland
Helena FONSECA	Portugal
Vlasta KAKOSOVA	Slovak Republic
Janez JAZBEC	Slovenia
Fernando DE ANDRÉS TRELLES	Spain
Marta GRANSTRÖM	Sweden

Julia DUNNE	United Kingdom

Alternates appointed by Member States or CHMP

Karl Heinz HUEMER	Austria
Jacqueline CARLEER	Belgium
Peter SZITANYI	Czech Republic
Sylvie BENCHETRIT	France
Birka LEHMANN	Germany
Pending	Greece
Brian AYLWARD	Ireland
Francesca ROCCHI	Italy
Herbert LENICKER	Malta
Johannes TAMINIAU	The Netherlands
Ine Skottheim RUSTEN	Norway
Jolanda WITKOWSKA-OZOGOWSKA	Poland
Hugo TAVARES	Portugal
Dana Gabriela MARIN	Romania
Viveca Lena ODLIND	Sweden

Members representing patients' organisations

Tsveta SCHYNS-LIHARSKA

Alternates representing patients' organisations

None

Members representing health care professionals

Adriana CECI

Jean Pierre ABOULKER

Anthony James NUNN

Alternates representing health care professionals

Paolo PAOLUCCI

Experts

Peter BAUER	Medical statistician

Observers

None

European Medicines Agency

Agnes SAINT RAYMOND	Head of Sector, Human Medicines Special Areas
Paolo TOMASI	Head of Section, Paediatric Medicines
Sophie OLIVIER	Scientific Administrator, Paediatric Medicines
Anne-Sophie HENRY-EUDE	Scientific Administrator, Paediatric Medicines
Blanca QUIJANO RUIZ	Scientific Administrator, Paediatric Medicines
Cecile OLLIVIER	Scientific Administrator, Paediatric Medicines
Dobromir PENKOV	Scientific Administrator, Paediatric Medicines
Elin Haf DAVIES	Scientific Administrator, Paediatric Medicines
Emilie DESFONTAINE	Scientific Administrator, Paediatric Medicines
Ermanno ZORZOLI	Scientific Administrator, Paediatric Medicines
Gunter EGGER	Scientific Administrator, Paediatric Medicines
Irmgard EICHLER	Scientific Administrator, Paediatric Medicines
Janina KARRES	Scientific Administrator, Paediatric Medicines
Peter KÁROLYI	Scientific Administrator, Paediatric Medicines
Ralf HEROLD	Scientific Administrator, Paediatric Medicines
Ralph BAX	Scientific Administrator, Paediatric Medicines
Richard VESELY	Scientific Administrator, Paediatric Medicines
Thorsten OLSKI	Scientific Administrator, Paediatric Medicines
Anna MESTERHAZY	Assistant, Paediatric Medicines
Aurelie HERVIEU	Assistant, Paediatric Medicines
Isabel PEREZ	Assistant, Paediatric Medicines