17 July 2013
EMA/PDCO/356146/2013
Human Medicines Development and Evaluation

Paediatric Committee (PDCO)

Minutes of the 12-14 June 2013 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 June 2013 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 June 2013 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 June 2013 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

III Discussion of applications

The PDCO discussed 89 procedures in total[1], of which:

- 40 paediatric investigation plan applications;
- 12 product-specific waiver applications;
- 5 compliance check procedures (interim and final);
- 32 requests for modifications of an agreed paediatric investigation plan.

IV Nomination of Rapporteurs and Peer reviewers

• List of letters of intent received for submission of applications with start of procedure August 2013[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 June 2013 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.

VI Discussion on the applicability of class waiver

Class waiver number	Active substance	Proposed indication	Condition	Outcome
EMEA-23-2013	BAN2401	Treatment of Alzheimer's Disease	Treatment of Alzheimer's Disease	Confirmed

[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).

EMEA-24-2013	RO5537381 (also known as GDC-0032)	Treatment of post-menopausal women with neoadjuvant or adjuvant breast cancer; treatment of postmenopausal women with advanced or metastatic breast cancer who have had recurrence or progression after treatment with an aromatase inhibitor	Treatment of breast carcinoma	Confirmed
EMEA-25-2013	Alisertib	Treatment of relapsed/refractory small cell lung cancer	Treatment of lung carcinoma (small cell and non-small cell carcinoma)	Confirmed
EMEA-26-2013	Alisertib	Treatment of relapsed/refractory epithelial ovarian cancer	Treatment of ovarian carcinoma (excluding rhabdomyosarcoma and germ cell tumours)	Confirmed

VIII Annual reports on deferrals

Annual report based on PIP decision for	Substances (abbrev.)	Product Name	Orphan drug	Difficulties progressing the PIP?	Outcome
EMEA-001167-PIP02-11	Atomoxetine hydrochoride	Strattera	No	No	The PDCO noted the report.
EMEA-000183-PIP01-08	Apixaban	Eliquis	No	No	The PDCO noted the report.
EMEA-000183-PIP02-12	Apixaban	Eliquis	No	No	The PDCO noted the report.
EMEA-000365-PIP01-08	Oseltamivir phosphate	Tamiflu	No	Yes	Recently, a modification of the PIP had been requested and changes had been agreed by the PDCO addressing the situation.
EMEA-000118-PIP02-10	Abatacept	Orencia	No	Yes	The applicant plans to submit a RfM
EMEA-000470-PIP01-08	Sitagliptin phosphate monohydrate	Januvia	No	No	The PDCO noted the report.
EMEA-000713-PIP02-10	Pixantrone dimaleate	Pixuvri	Yes	No	The PDCO noted the report.
EMEA-000429-PIP01-08	N. meningitidis serogroup Y, W, C and A polysaccharides, conjugated to tetanus toxoid	Nimenrix	No	Yes	Applicant experiences recruitment difficulties in the last 2 studies of the agreed PIP. A modification procedure has been filed.
EMEA-000065-	Telbivudine	Sebivo	No	No	The PDCO noted the

Annual report based on PIP decision for	Substances (abbrev.)	Product Name	Orphan drug	Difficulties progressing the PIP?	Outcome
PIP01-07					report.
EMEA-000116-PIP01-07	Retigabine	Trobalt	No	No	The PDCO noted the report.
EMEA-000412-PIP01-08	Insulin detemir	Levemir	No	No	The PDCO noted the report.
EMEA-000434-PIP01-08	Ambrisentan	Volibris	Yes	Yes	Paediatric studies are on hold in Europe due to unexpected findings in a juvenile rat study. Data is under review by CHMP rapporteur. A report is expected by end of July.
EMEA-000145-PIP01-07	Denosumab		No	No	The PDCO noted the report.
EMEA-000145-PIP02-12	Denosumab	Xgeva (previously Amgiva), Prolia	No	No	The PDCO noted the report.
EMEA-000308-PIP01-08	Rituximab	MabThera	No	No	The PDCO noted the report.
EMEA-000157-PIP01-07	Belatacept		No	No	The PDCO noted the report.
EMEA-000235-PIP02-10	Aripiprazole	Abilify	No	No	The PDCO noted the report.
EMEA-000568-PIP01-09	C1 Inhibitor	Cinryze	Planned	Yes	The modification opinion was adopted at this plenary meeting
EMEA-000601-PIP01-09	Pazopanib		Yes	No	The PDCO noted the report.

IX Other topics

Guidelines	
Contribution of PDCO to scientific guidelines	For the discussion of guidelines, PDCO members will be systematically involved and the committee will be informed about progress of the guidelines.
Guideline on pharmaceutical development of medicines for paediatric use	This guideline is expected to be adopted by the Quality Working Party and then, in July by the PDCO, before being adopted by the CHMP.
Working groups	
Formulation	No non-product related issues where reported to the Committee.
Non-Clinical	Documents tabled for information
Paediatric oncology	Product-specific discussions were prepared by the group.

Paediatric Inventory of Therapeutic Needs	Discussion on the therapeutic area of nephro-urology.
Extrapolation	N/A
Other topics	
Summary of the current practice within the PDCO FWG with regards to the acceptance criteria	Document presented by the Quality of Medicines sector colleagues will be added to the postmail for comments.
Screening criteria for PIPs. Examples of key binding elements (quality).	The Quality of Medicines colleagues presented the screening criteria for discussion of formulations by the FWG and the current practice within PDCO FWG with regards to acceptance criteria.
Summary of Opinion template and guidance*	The template and guidance will be sent to PDCO members in the postmail, for adoption in the July meeting.
Paediatric Inventory	The drafting of the inventory for the therapeutic area nephro-urology was completed and discussed.
Vaccine schedules in PIPs* - Update	The European Commission (DG Sanco-Directorates C and D) and ECDC have received a letter from EMA informing them about the project and asking for nomination of a contact point to start the collaboration. The project will be presented in June to the relevant EMA Scientific Committees, for information. Feedback from the presentation at the Vaccines Working Party on 07 June 2013 was provided to the PDCO members.
Good Clinical Practice (GCP) inspections of paediatric clinical trials agreed in Paediatric Investigation Plans	The PDCO welcomed the greater interaction planned between Inspectors and the Committee, particularly to enhance understanding of the problems related to clinical trials in children. The discussion paper has been added to these minutes for information.
CHMP update on paediatric topics	New paediatric indications granted at May CHMP meeting were presented to the PDCO.
Reflection on class waiver revocation	The PDCO suspends, for a limited period of time, the review of the condition class waivers that had been initiated in 2012. The handling of class-waived conditions is now being seen in conjunction with the definition of the scope of a PIP and with condition(s) in orphan designations. These topics are complex and interrelated. The Agency with its scientific committees needs more time to progress with the topics. The PDCO did not adopt an opinion changing the condition class waivers during this meeting. The EMA with its Paediatric Committee have decided to integrate its approach to transparency in paediatric activities and to the definition of the condition. A public consultation on a comprehensive draft policy is planned.

Discussion on role and benefit of PDCO informal meetings	The feasibility of a potential join PDCO-COMP-CAT informal meeting in November was discussed.
Candidature to the election of Chair and Vice-Chair	The election of new PDCO chair and co-chair will take place at the beginning of the September meeting. A call for candidatures was extended to the PDCO delegates.

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 June 2013

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 evaluation form	Topics on the current Committee Agenda for which this restriction applies
Adriana Ceci	Restriction level 3	EMEA-001315-PIP01-12
Adriana Ceci	Restriction level XR	EMEA-000019-PIP09-13
Alexandra Compagnucci	Restriction level XR	EMEA-001464-PIP01-13
Alexandra Compagnucci	Restriction level XR	EMEA-000019-PIP09-13
Alexandra Compagnucci	Restriction level XR	EMEA-001457-PIP01-13
Alexandra Compagnucci	Restriction level XR	EMEA-001469-PIP01-13
Alexandra Compagnucci	Restriction level XR	EMEA-000117-PIP01-07-M05
Alexandra Compagnucci	Restriction level XR	EMEA-000689-PIP01-09-M04
Carine de Beaufort	Restriction level XR	EMEA-001464-PIP01-13
Carine de Beaufort	Restriction level XR	EMEA-001053-PIP02-13
Carine de Beaufort	Restriction level XR	EMEA-000430-PIP01-08-M04
Carine de Beaufort	Restriction level XR	EMEA-001425-PIP01-13
Carine de Beaufort	Restriction level XR	EMEA-001469-PIP01-13
Carine de Beaufort	Restriction level XR	EMEA-001441-PIP01-13
Carine de Beaufort	Restriction level XR	EMEA-001434-PIP01-13
Christoph Male	Restriction level XP	EMEA-000430-PIP01-08-M04
Christoph Male	Restriction level XP	EMEA-001456-PIP01-13
Christoph Male	Restriction level XP	EMEA-001114-PIP01-10-M01
Christoph Male	Restriction level XP	EMEA-000914-PIP01-10-M01
Dobrin Konstantinov	Restriction level DP	EMEA-000019-PIP09-13

Member, alternate, expert name	Outcome restriction following evaluation of electronic evaluation form	Topics on the current Committee Agenda for which this restriction applies
Gerard Pons	Restriction level DP	EMEA-000467-PIP01-08-M03
Jaroslav Sterba	Restriction level XP	EMEA-001429-PIP01-13
Jaroslav Sterba	Restriction level XP	EMEA-000019-PIP09-13
Jean-Pierre Aboulker	Restriction level XR	EMEA-001464-PIP01-13
Jean-Pierre Aboulker	Restriction level XR	EMEA-000019-PIP09-13
Jean-Pierre Aboulker	Restriction level XR	EMEA-001457-PIP01-13
Jean-Pierre Aboulker	Restriction level XR	EMEA-001469-PIP01-13
Jean-Pierre Aboulker	Restriction level XR	EMEA-000117-PIP01-07-M05
Jean-Pierre Aboulker	Restriction level XR	EMEA-000689-PIP01-09-M04
Kolbeinn Gudmundsson	Restriction level DP	EMEA-001348-PIP01-12
Matthias Keller	Restriction level DP	EMEA-001351-PIP01-12
Michal Odermarksky	Restriction level XP	EMEA-001460-PIP01-13
Michal Odermarksky	Restriction level XP	EMEA-001442-PIP01-13
Michal Odermarksky	Restriction level XP	EMEA-000317-PIP01-08-M04
Michal Odermarsky	Restriction level XP	EMEA-001368-PIP01-12
Michal Odermarsky	Restriction level XP	EMEA-000222-PIP01-08-M07
Paolo Rossi	Restriction level DP	EMEA-000830-PIP02-10-M01
Paolo Rossi	Restriction level XR	EMEA-001442-PIP01-13
Paolo Rossi	Restriction level XR	EMEA-001429-PIP01-13
Paolo Rossi	Restriction level XR	EMEA-001469-PIP01-13
Paolo Rossi	Restriction level XR	EMEA-001441-PIP01-13
Paolo Rossi	Restriction level XR	EMEA-001430-PIP01-13
Paolo Rossi	Restriction level DP	EMEA-000872-PIP02-13

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:

Evaluation of the conflict of interest	
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 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 June

List of Participants

Chair

Daniel BRASSEUR

Vice-chair

Dirk MENTZER

Members appointed by Member States or CHMP

Christoph MALE	Austria
Koenraad NORGA	Belgium
George SAVVA	Cyprus
Jaroslav STERBA	Czech Republic
Marianne ORHOLM	Denmark
Irja LUTSAR	Estonia
Pirjo LAITINEN-PARKONNEN	Finland
Gerard PONS	France
Dirk MENTZER	Germany
Agnes GYURASICS	Hungary
Gylfi OSKARSSON	Iceland
Kevin CONNOLLY	Ireland
Paolo ROSSI	Italy
Carine de BEAUFORT	Luxembourg
Hendrik van den BERG	The Netherlands
Siri WANG	Norway
Marek MIGDAL	Poland
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
Ann Marie KAUKONEN	Finland
Sylvie BENCHETRIT	France
Birka LEHMANN	Germany
Francesca ROCCHI	Italy
Johannes TAMINIAU	The Netherlands
Jolanda WITKOWSKA-OZOGOWSKA	Poland
Hugo TAVARES	Portugal
Dana Gabriela MARIN	Romania
Maria Jesus FERNANDEZ CORTIZO	Spain
Viveca Lena ODLIND	Sweden
Angeliki SIAPKARA	United Kingdom

Members representing patients'

Michal ODERMARSKY

Members representing health care professionals

Anthony James NUNN

Alternates representing health care professionals

Paolo PAOLUCCI

European Medicines Agency

Paolo TOMASI	Head of Section, Paediatric Medicines
Sophie OLIVIER	Scientific Administrator, Paediatric Medicines
Anne-Sophie HENRY-EUDE	Scientific Administrator, Paediatric Medicines
Almudena SAIZ HERRANZ	Scientific Administrator, Paediatric Medicines
Benjamin PELLE	Scientific Administrator, Paediatric Medicines
Chrissi PALLIDIS	Scientific Administrator, Paediatric Medicines
Dobromir PENKOV	Scientific Administrator, Paediatric Medicines
Elin Haf DAVIES	Scientific Administrator, Paediatric Medicines
Emilie DESFONTAINE	Scientific Administrator, Paediatric Medicines
Giovanni LESA	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
Alessandro JENKNER	National Expert on Secondment, Paediatric Medicines
Cristina BEJNARIU	Trainee
Aurelie HERVIEU	Assistant, Paediatric Medicines
Aneta KRZYSCIAK	Assistant, Paediatric Medicines
Sunni HOLTMAN	Assistant, Paediatric Medicines

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

23 July 2013
EMA/PDCO/356146/2013EMA/701331/2012
Human Medicines Development and Evaluation

Discussion paper on GCP inspections of paediatric clinical trials agreed in Paediatric Investigation Plans

1. Introduction

Good Clinical Practice (GCP) inspections are performed to verify that clinical trials have been designed, conducted, documented and reported in accordance with international ethical and scientific quality standards, providing public assurance that the rights, safety and well-being of trial subjects are protected and that the clinical trial data are credible. These inspections are conducted in accordance with Article 15 of Directive 2001/20/EC.

The National Regulatory Authority and the ethics committee with jurisdiction for the investigator site(s) in the country where the trial takes place have responsibility for the authorisation and supervision of clinical trials in their country. Within the EU/EEA the authorisation of clinical trials is the responsibility of the National Regulatory Authorities, and ethics committee(s) in the Member State(s) where the sponsor wishes to conduct the clinical trial, in accordance with the clinical trial Directive 2001/20/EC. Similarly, for a clinical trial to be conducted in a non-EU/EEA country the sponsor must seek permission from the National Regulatory Authority and ethics committee(s) in each country where they wish to carry out the trial. EU/EEA authorities have no jurisdiction over the conduct of clinical trials being carried out in non EU/EEA countries.

GCP inspections may be performed as part of the supervision of authorised clinical trials in Europe or in the context of Marketing Authorisation Applications (MAAs). In this last case, inspections may involve sites outside the EU. In both cases GCP inspections are carried out by Member States' inspectorates in accordance with Article 15 of Directive 2001/20/EC.

In the context of the centralised procedure, inspections are coordinated by the European Medicines Agency and two types of GCP inspections are possible, routine and triggered.

Routine inspections are requested as part of the on-going surveillance of the quality of studies received in MAAs and proposed by the Compliance and Inspections sector after GCP validation. Triggered inspections are requested when the assessors identify specific concerns with the report and data on a trial which they consider needs a specific investigation by inspection. Both types of inspection will be adopted by the Committee for Human Medicinal Products (CHMP), which will evaluate their reports as part of the assessment process.

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In the context of GCP inspections and the Paediatric Committee (PDCO) as discussed in this paper, such inspections would always be triggered inspections themselves.

The PDCO has identified, in limited cases, the need to clarify issues related to paediatric clinical trials. This paper tries to identify ways for the PDCO to meet its needs and

- explains what is the focus of GCP inspections;
- explores if and when the PDCO could trigger inspections;
- explores ways for the PDCO to signal potential GCP issues in clinical trials agreed in Paediatric Investigation Plans (PIPs).

2. Could the PDCO directly request GCP inspections?

Member of the Regulatory Affairs sector and of the Compliance and Inspections sector at the EMA clarified that the PDCO does not have direct supervisory role over the conduct of the clinical trials agreed in a PIP, which remain, as adult clinical trials, under the control of the National Regulatory Authorities of the Member State(s) where they take place, or their equivalent in third (non-EEA) countries. However, by clarifying the roles and responsibilities of all parties involved and in particular those with responsibility for the authorisation and supervision of clinical trials, clear processes can be established, to enable the PDCO to communicate concerns about GCP compliance to the relevant authority and to ask if a GCP inspection can be carried out. Thus, the PDCO may identify triggers for inspections that can be communicated:

a) to the Member States concerned, through the Compliance and Inspection sector, for them to consider the coordination of a GCP inspection as part of their supervision of clinical trials

or

b) to the Compliance and Inspection Sector at EMA for consideration in the case the concerned clinical trial is part of a centralised marketing authorisation dossier to be assessed by the CHMP.

Therefore, clear processes can be established to ensure that PDCO concerns are properly communicated and to identify whether further actions are considered necessary. A Standard Operating Procedure should specify the steps to be taken by the PDCO to communicate their potential concerns and triggers for a GCP inspection.

3. Scope of GCP inspections

When the PDCO has concerns that certain aspects of clinical trials agreed in a PIP are not carried out properly; it is important to know whether these concerns are of GCP-nature (and therefore relevant to a GCP inspection) or of different nature, which should then be addressed by other means, such as questions to the applicant.

The scope of GCP inspections is to determine whether good clinical practice standards, and related rules, have been adhered to for the conduct of the clinical trials. GCP inspections cannot be triggered if the concern is a non-compliance outside of the scope of GCP standards (e.g. to determine why the applicant is not performing a clinical trial that was required by an agreed PIP). As an example, in Annex I a standard scope of a routine GCP inspection is shown.

4. GCP issues that could arise in paediatric clinical trials

GCP-related issues in paediatric clinical trials have been reported in the past. In one case, GCP inspections were performed, due to concerns on the quality of the data, by National Regulatory Authority inspectorates as part of the supervision of authorised clinical trials. The focus of the inspections was on primary endpoints and on safety. GCP inspectors visited the sponsor site as well as two investigator sites and found several critical failures (i.e. resulting in rejection of data and/or legal action) including lack of definition on how to measure the primary endpoint, evaluation of a laboratory assay by different operators with different techniques, judging a primary endpoint differently by different operators and failure to refer patients to the independent review committee. In addition, several major failures (i.e. resulting in possible rejection of the data and/or legal action) were reported, including failure to report some diagnosis on case report forms and delegating diagnosis and reporting to investigators, failure to record some relevant lab values for patient monitoring, failure to assess causality or severity of serious adverse events and major delays in reporting serious adverse events.

A problem that applicants seem to encounter quite often in paediatric clinical trials is related to patient recruitment. In some cases, the PDCO could have concerns that the applicant has not done enough to carry out the trial with the patient population agreed in the PIP. In these cases the issue is beyond the scope of GCP inspection, and therefore not the correct regulatory tool for determining whether or not an applicant is genuinely trying to perform a trial, or whether the trial itself is feasible. One effective approach would be for the PDCO to ask specific questions directly to the Company when PIP modifications of an agreed PIP are requested or at the time of the annual report[2].

5. Consideration of the inspection outcome during the PIP procedure

In case the PDCO identifies triggers for a GCP inspection to be communicated and performed as outlined in section 2, point (a), it should be noted that this inspection can take approximately 4-6 months from when the problem is flagged to when the final report is completed, depending on where the clinical trials take place and on the number of sites to be inspected. Because of the timeframe involved, it has to be noted that an inspection report could realistically be finalised before the finalisation of a PIP application only if the inspection is performed before day 30 of the PIP procedure. Not enough time would be available during shorter procedures, such as modifications (60 days) and compliance checks to have a final inspection report before the closure of the modification of an agreed PIP or compliance check procedure. Even in the case of 120-day long procedures, the timing is very tight and in several cases —when the clock-stop is short, for example— it is likely that the report would not be finalised before the finalisation of the PIP application.

It is also important to determine what action the PDCO can take if they are aware of GCP non-compliance identified during a GCP inspection. In summary, a) the PDCO could not agree to include the study in the PIP; b) if the negative inspection report is received after the PIP decision and the

[2] The questions to be asked to the applicant will depend on the reasons put forward to justify inability to complete the agreed PIP. For example, quite often applicants claim that they are unable to recruit enough patients in their clinical studies. Common failures that could result in low recruitment are the following:
Poor selection of investigator sites
Example of possible requests of clarification to the applicant:
a) How many sites were selected?
b) What is the investigator's experience with clinical trials?
c) What was patient recruitment by the same investigators in other trials?
d) Was a proper advertising campaign carried out (and approved by ethics committee)?
Poor protocol design/poor study feasibility
Example of possible requests of clarification to the applicant:
e) Provide study protocol
f) Provide details on how the study was planned

study is already included in the PIP, the PDCO could, for instance, inform the CHMP or the National Regulatory Authority in charge of the clinical trial application/MAA evaluation; c) if the PDCO determines that the GCP infringements result in the PIP not being compliant, the compliance check will be negative.

It is to be noted that the above is without prejudice to any liability or other sanctions that may be associated with GCP failures under national law.

6. How to prioritise GCP inspection

On occasion, the EU National Regulatory Authorities might establish prioritisation of GCP inspections. Experience accumulated over the years by several Inspection Authorities (the Medicines and Healthcare products Regulatory Agency, for example) has shown that prioritisation should be implemented depending on the potential risks posed by the GCP non-compliance. Thus, the PDCO, in cooperation with the Compliance and Inspections sector, should rank the GCP concerns by carrying out risk assessments and categorising them as high, medium and low risk. The risk assessment should evaluate the parameters reported in Annex II. Briefly, this assessment would take into account the potential risks a) posed to participant safety associated with the type of medicinal product, b) associated with design and methods of the trial and c) associated with the history of GCP non-compliance of the sponsor. The steps that the PDCO should follow to communicate the need for GCP inspections are shown in Annex III.

7. PDCO input in the scope of GCP inspections concerning paediatric clinical trials requested by the CHMP

Paediatric Investigation Plans include paediatric clinical trial programs that have been agreed with the PDCO. At the time of MAA in the context of the centralised procedure, the CHMP could request inspections of paediatric clinical trials, either on their own initiative or because alerted of potential GCP non-compliance by another stakeholder, for instance the PDCO. In the second case the PDCO could provide advice on the potential GCP non-compliance issues related to paediatric development and in both cases it could be consulted and provide their view to the CHMP. For this reason it would be advisable that the PDCO is informed when the CHMP requests paediatric trials to be inspected. To this end, the EMA Compliance and Inspections sector could alert the Paediatric Coordinator in charge of the product who, in turn, could immediately inform the PDCO delegates concerned to get information on potential issues about the trial for consideration in the scope of the inspection to be adopted by the CHMP and for verification by the inspectors during the conduct of the inspection. The list of marketing authorisations containing paediatric clinical trials subject to inspection will be included in the PDCO agenda for information or discussion, as applicable. The EMA Compliance and Inspections will also inform the PDCO on the outcome of the inspection and will circulate the final inspection report.

Annex I
Scope of a routine GCP inspection

The inspection focuses in the verification of selected efficacy and safety data reported in the Marketing Authorisation Application for a sample of patients to be determined by the inspectors.

The inspectors are asked in particular to focus on confirming:

A. At the Investigator site:

- Verify the existence of the patients
- The availability of informed consent for each patient in the sample and the procedure to obtain this consent
- Verification of the method used to assess the primary efficacy measurement
- Adherence to inclusion and exclusion criteria
- Source data verification on baseline data and endpoints and in particular with focus on:

  Efficacy at time points identified in the protocol

  Safety at time points identified in the protocol
- Verification of the administration of study medication administration and accountability
- Reporting of serious adverse events
- Confirmation of the monitoring of the study by the sponsor.

B. At the Sponsor site:

- Distribution of sponsor's duties or functions and among Clinical Research Organisations acting on their behalf (when applicable)
- The procedures for the Data and Safety Monitoring Board or any other relevant Committees for the clinical data review (when applicable)
- Investigator selection and agreements
- The monitoring process
- The documentation on the investigational medicinal product
- The randomisation process, when applicable
- Collection, review, follow up and reporting of serious adverse events
- The decision making process for the allocation to the ITT and PP populations
- The collection, handling and clarification/correction of study data
- The compliance with the protocol and statistical analysis, including further amendments
- The process for the interim and final database lock and the unblinding when applicable
- The process to ensure that the clinical study report is an accurate reflection of the conduct of the clinical trial
- The relevant aspects of the trial master file
- The sponsor audit and the quality assurance system

Annex II
Risk assessment to GCP inspections of paediatric trials

1. Risk to participant safety associated with the medicinal product
    a) Nature of the medicinal product
    b) Potential toxicities
    c) Body system that may be affected
    d) Monitoring that would need to be done
    e) Study population includes particularly vulnerable groups
    f) Use in combination with other medications with consequent increased risk of toxic effects
    g) Anticipated safety issues
    h) Potential risk of dosing errors(formulation not tailored to children)
    i) Lack of juvenile animal studies in the Paediatric Investigation Plan

2. Risk associated with design and methods of the trial
    a) Risk to participant safety due to clinical procedures specified in the protocol
        i. Protocol includes investigations or other clinical procedures that carry significant risk
        ii. Protocol includes additional procedures over and above those expected from standard care
        iii. Protocol includes adults and children and is designed for adults
        iv. Likelihood and severity of the harm that could be caused to participants
        v. Potential measures that could reduce the likelihood or severity of harm to the study participants
        vi. No measures to reduce distress are planned
    b) Risks to participant rights from failure to obtain fully informed consent
        i. Does study population include vulnerable groups (for example, neonates or patients with mental health problems)?
        ii. Participants likely to lack capacity to give fully informed consent?
        iii. Who will decide whether or not a participant is capable of giving consent?
        iv. What measures might reduce the likelihood that participants might be included in the study without the appropriate level of consent?
    c) Risks to participant rights from failure to protect personal data
        i. Are particularly sensitive data being collected?
        ii. Are personal identifiers associated with the data?
        iii. Will consent of the participant to access and use the data be obtained?

iv. If study takes place outside of the EU, are data protections equivalent to those in the EU?

v. Has consent been given to share data with third parties?

vi. Are data security measures appropriate to the types of data?

vii. Is assent required and from what age?

3. Risk associated with applicant

   a) Lack of GCP compliance in previous inspections

   b) History of failure to comply with agreed PIPs

   c) Unusually high number of modifications to an agreed PIP

4. Risk associated with applicant

   Risk with trial site or investigator

   i. High number of simultaneous trials

   ii. No previous inspection

   iii. Participation in neonatal trial but no neonatal treatment centre

   iv. Single or one of very few sites in trial primarily conducted in third Countries

Annex III – Decision tree to communicate the need for GCP inspections