EUROPEAN COMMISSION
HEALTH AND CONSUMERS DIRECTORATE-GENERAL

Health systems and products
Medicinal products – quality, safety and efficacy
Head of Unit

Brussels,
SANCO/D6

MINUTES OF THE MEETING OF THE AD HOC GROUP ON CLINICAL TRIALS

**'Centre de Conference Albert Borschette' CCAB,
Room AB-4B, rue Froissart 36,
1040 Brussels.
1 December 2014, from 10.00 h.**

1. Welcome

The Commission representative (COM) welcomed the participants. COM informed that the tentative days of the ad hoc group meetings in 2015 are 9 March, 20 April, 8 June, 25 September and 3-4 November. The dates will be confirmed 6 weeks before the meeting. COM also announced that the invitations to the ad hoc group meeting will be sent to the nominated experts, but also to permanent representations.

2. Adoption of the draft agenda

The agenda was adopted without changes.

3. Adoption of the minutes of the meeting held on 6 June 2014.

The minutes were adopted without amendments.

4. Update by EMA on the development of the EU CT Portal and Database

EMA gave presentation updating the group on the progress of the development of the EU Portal and Database. The presentation gave an overview of the project and timelines for key milestones. The main focus of the EMA presentation was to report on the changes made in the document on Functional Specification after the public consultation. EMA informed that the revised document would be presented for adoption during the next EMA Management Board meeting on the 17 and 18 of December. EMA also informed that the Addendum to the Functional Specification on transparency will be submitted to the Member States and Commission to comment in the days following the ad hoc group meeting. The meeting with all Member States to discuss the comments will be held on 13 January 2015. Following this a short public consultation will be carried out. The intention is to submit the final document for the adoption by EMA Management Board in March 2015 .

Certain delegates (DE, ES) and COM expressed their concerns as regards the timelines for the addendum on transparency, stressing in particular that the time for commenting is very short.

As regards the revised Functional Specification document some participants requested more clarification on what will be the exact scope of the audit, in particular whether the interaction of the CT Portal with the CT Eudravigilance Module will be audited. EMA clarified that the CT Eudravigilance module will not be in the scope of the audit.

5. Working document on the detailed arrangements for the inspection procedures including qualification and training requirements of inspector, in preparation for a Implementing Regulation by the Commission

The discussion on items 5 and 6 were preceded by a presentation of the general timelines for the adoption of the Implementing and Delegated Regulations.

The COM introduced the working document explaining that it was drafted with the intention to carry over, to the extent possible, the relevant provisions of Commission Directive 2005/28/EC on Good Clinical Practice, as agreed during the last ad hoc group meeting, and adapting the text to the legal form of a Regulation. The comments, received from the ad hoc group as well as from EMA GCP inspectors working Group, were taken into account. COM stressed that the document has not been scrutinized by the Legal Service (LS) of the Commission. However COM followed the LS instructions and for that reason any reference to the guidelines were removed.

Following the general introduction a presentation was given of the working document section by section, followed by comments and discussion.

The ES delegate noted, as regards section 1, that there is a redundancy in the proposed wording. This was acknowledged by the COM who informed that the text will be amended. The AT delegate asked whether the regulation could apply in context of inspections related to non-interventional studies. COM replied that the legal basis for the regulation does not provide for that.

COM explained that section 2 was slightly amended in order to accommodate the ad hoc group request to introduce the requirement of adequate experience of the inspectors.

There were no comments on sections 3 and 4. COM explained that the latter is a new provision which was proposed to reflect the provisions of Article 15 of Directive 2001/20/EC not carried over to Regulation (EU) 536/2014 and specifying the potential remit of GCP inspections.

As regards section 5 the UK delegate proposed to introduce in paragraph (1) a clarification that it is possible to perform a GCP inspection even if a CT is not published. COM considered that the proposed wording is broad and covers all stages of the clinical trials, including the reporting phase. EMA suggested aligning the wording in paragraph (2) with the wording in the new Pharmacovigilance legislation regarding the role of EMA in coordinating the cooperation between Member States on inspections. EMA also proposed to include the possibility for a Member State to request assistance from another Member State.

The DE expert asked for clarification on the purpose of paragraph (3) of section 5. COM explained that this provision intends to give a formal basis for further cooperation between the Member States and the Commission on the GCP

guidelines. COM drew to the attention of the group that an explicit reference to guidelines was deleted from the working document. This reference was replaced by the term "commonly recognized standards" which is also clarified in the proposed recital, and refers to the legacy of Directive 2005/28/EC encompassing the guidelines.

COM asked, as regards section 6, how the term *'documents relating to adoption of good clinical practice principles*' taken over from Directive 2005/28/EC is interpreted in the Member States. The PL delegate clarified that in Poland this term would encompass all national provisions relating to GCP. In Poland the national legislations incorporate the provisions of GCP guidelines. The inspectors, when performing their duties, refer to binding law and not to the guidelines. In this context the PL delegate, supported by some other delegations, raised the question whether under the new legislative framework of Regulation (EU) 536/2014 a Member State can continue this practice. COM clarified that the new clinical trials rules are in a legal form of Regulation and are therefore directly applicable. The ICH guidelines are referred to in Article 47 of the Regulation and shall also be taken into appropriate account by the sponsor and investigor when drawing up the protocol. COM recalled that this issue was intensively discussed during the negotiations of the Regulation. The Member States cannot overcome this limitation by adopting the ICH guidelines as a national law. However, COM will check with internally whether it is possible to allow national legislation on general GCP principles, on the condition that it complies with the Regulation. COM, replying to the ES delegate's question, clarified that the ICH guidelines will be made available on the Commission website as Article 47 stipulates. This does not change their legal character, they remain not legally binding.

EMA proposed to carry over the relevant wording of Article 24 of Directive 2005/28/EC regarding the right of access since it provided a clearer text. ..

There were no comments on section 7.

As regards section 8 the DE delegate raised the question whether the new Implementing Regulation should not provide for more harmonization among Member States and a common Union procedure for GCP inspections. In this respect COM stressed that the advice so far received from the ad hoc group and from the EMA GCP Inspectors Working Group was to maintain the status quo, whereby the details of the procedures are established at the national level. COM invited all experts to reflect on the DE delegate's suggestion.

There were no comments on section 9.

As regards the section 10, COM drew to the attention of the group that in line with Regulation (EU) 536/2014, the inspecting authority will be obliged to submit the inspection report via the EU Portal. The IT delegation enquired who will have access to the inspection report. EMA clarified that in principle it will be the sponsor and the other Member States concerned who will have access. However it is not excluded that it will be available to the general public at some stage. This will be discussed together with other transparency issues.

The AT and UK delegates commented on the provision proposed in section 10 relating to the obligation to keep all records of national and international inspections, independently of the obligation to submit the inspection report (referred

to above) via the EU Portal. They stressed that it is too broad and it is not clear how long the records should be kept. COM clarified that in absence of any specific provision the national law on archiving would apply. COM will consider introducing a provision aligning this period of time with that referred to in article 58 of the Regulation for the archiving of the master file.

The ES delegate mentioned that there is possibly some redundancy in section 11 as section 1 refers already to confidentiality rules.

As regards section 12, concerning the Union Controls, delegates made a general comment that the provision could refer to experts in general and not only to inspectors. COM proposed to discuss this issue under item 8 of the Agenda, related to Union controls.

COM concluded the discussion by informing the group that the working document will be reviewed in light of the ad hoc group comments, including the ones received after the meeting. COM made a call for written comments, reminding them specifically on the issue raised by DE regarding the introduction of a provision setting a common procedure for inspections rather than having separate ones at the national level.

6. Working document on Good Manufacturing Practices for Investigational Medicinal Products, in preparation for a Delegated Regulation by the Commission

COM gave a brief introduction to the working document that had been drafted on the basis of the provisions on investigational medicinal products of Directive 2003/94/EC and comments received from this group and the GCP and GMDP IWGs. A reservation was taken because the working document had not yet been through scrutiny by the LS. COM highlighted the sections on which specific feedback from the group was requested.

The working document was surveyed by the group and no comments were given on sections 1, 5-7, 9-11, 13, 15 and 18.

COM explained that the delegated regulation on GMP for investigational medicinal products will set out the high-level principles while the guideline on GMP for investigational medicinal products as referred to in Art. 63 of Regulation (EU) 536/2014 will set out the details; the situation will be similar to the existing one with Directive 2003/94/EC and Annex 13. COM also clarified that placebo would also be covered by the delegated regulation on GMP for investigational medicinal products.

With regard to section 2 on the definition of pharmaceutical quality system, the DE and UK delegates expressed support to the alternative proposal which took into consideration the revision of Chapter 1 of the EU GMP Guide and the ICH Q10 guideline.

COM requested some feedback from the group on the proposed definition of manufacturer because it does not seem to fit for purpose in all sections where it is used. However, should it stay in the working document, it would cover both physical and legal persons.

COM expressed concerns that section 3(2), 2nd subparagraph might be an additional requirement on the importer that could not be included in the delegated regulation on GMP for investigational medicinal products. The UK delegate thought that the provision might possibly be deleted, while the DE delegate wished to keep it as practical experience has shown that it was useful.

On section 4, the IE delegate requested that the role of the sponsor should be mentioned in the section as the one ultimately responsible for the clinical trial, including for GMP for the investigational medicinal products, is the sponsor. COM found it in general difficult to put obligations on the sponsor in the delegated regulation on GMP for investigational medicinal products because GMP concerns manufacturing and import, which are activities not necessarily carried out by the sponsor.

COM raised two issues with regard to section 8(1), 2nd subparagraph in relation to the retention period of batch documentation and the obligation to retain records in accordance with Annex I to Directive 2001/83/EC.

A proposal had been made by a Member State that the manufacturer should retain batch documentation as essential information for 25 years in line with the requirement to retain the clinical trial master file for 25 years which seemed like a heavy burden on the manufacturer. COM asked if it would be possible that the batch documentation could be transferred to the sponsor for retention in line with retention period for the clinical trial master file; the AT and DE delegates did not favour of such possibility and the DE delegate thought that the current 5 years of retention after completion or discontinuation of the clinical trial were sufficient.

The other issue raised was that the possible deletion of the obligation of the sponsor or marketing authorisation holder to retain records for marketing authorisation in accordance with Annex I to Directive 2001/83/EC as such obligation was not a GMP matter; the group did not object to this.

A short discussion took place on Section 12(1) and the procedures for recall where the DE delegate thought that in case of recall a harmonised approach would be necessary to act swiftly and the UK delegate added that any provisions in the delegated regulation should be consistent with Chapter 8 of the EU GMP guide. It was suggested that this issue be discussed with the GMDP IWG.

With regard to Section 12(2) the manufacturer has to have a procedure for unblinding where that is necessary for a recall. The sponsor's responsibility for unblinding relates to the individual patient, but the manufacturer may need to unblind to determine the product used and for traceability because of safety problems of one patient.

COM drew attention to a new provision in section 14 allowing for GMP to be adapted to the special characteristics of advanced therapy investigational medicinal products. The intention of the provision was welcomed by the AT delegate but some concern was expressed as to the wording mixing data requirements with the risk based approach.

COM explained that the different approaches with regard to the empowerment of inspectors for GCP and GMP as expressed in section 16 were due to the fact that GMP and GCP had sprung from directives that were different in this respect. The

DE delegate supported that the competence for GMP inspectors were aligned to the principles already established by Directive 2001/83/EC.

On the competences of GMP inspections set out in section 17 it suggested that in the first bullet point inspectors should have documented experience, in the second bullet point that a reference be made to advance therapy medicinal products as these require special expertise. The DE delegate will send a written proposal for a slight amendment of the fourth bullet point.

COM clarified that for measures to be taken according to section 19 against the manufacturing authorisation referred to in Art. 61(1) of REG 536/2014 an EU inspection would be required, unless inspections by 3rd countries were covered by a MRA.

COM informed about the plans to draft in parallel a new Implementing Directive on GMP for finished products to replace Directive 2003/94/EC. Such new directive should be applicable at the same time as the Clinical Trial Regulation.

The next steps in the drafting of the Delegated Regulation are written comments from this group and following a redraft of the working document a consultation of the GMDP IWG is anticipated, possibly coinciding with the GMDP IWG meeting in March 2015.

7. Draft text of the revised Q&A document on the CT Regulation

COM explained the process for updating the Question and Answer document to bring it in line with the Clinical Trials Regulation. This included update of relevant information that was amended by the Regulation, incorporation of relevant parts of CT1, references to the CTR. Quite a number of new Q&As were also added.

COM highlighted that this will be a "living" document with further Q&As being added and updated as necessary. For example, COM stated that differences between the Directive and Regulation may also be included in the document, where relevant.

Additionally, certain Member States had put forward particular proposals to be included in the Q&A.

In this respect COM asked the group for support to provide relevant responses. These mainly regard:

- -How to deal with the provisions on cluster randomised trials;
- Some GLP issues;
- Timing for the input of the results from the sub-study.

COM also asked the group to put forward any other Q&As they consider necessary.

A discussion followed on the questions on which specific feedback from the group was requested by the COM. With regards to Question 2.5 on whether a change to documentation submitted to Member States during ongoing assessment would be considered to be a substantial modification, some delegates emphasised that sponsors should not be allowed to submit new documentation. Changes to documentation should only take place upon request by Member States if they consider the need for additional information during assessment. Therefore it was agreed that the question was no longer relevant under the Regulation.

The response to question 2.9 regarding whether it is possible to submit an application limited to Part I only with regards to some of the Member States concerned, was discussed. The group agreed with the possibility of having mixed application. COM clarified that the "decision" referred to in the last sentence regarded that of Part I of the application in the case of Member States where Part II had yet not been submitted.

A discussion was held on question 2.10 regarding whether a sponsor is allowed to submit a substantial modification concerning Part I in all Member States, also in those Member States where an application was originally submitted for only Part I (limited application on the basis of Article 11). Certain delegates asked about the interpretation of the definition of a substantial modification COM clarified that the definition sets the condition that before a substantial modification can be submitted all Member States Concerned should have taken a decision on Part I. Therefore the assessment of a substantial modification concerning Part I should take place in all Member States that have issued positive conclusions on Part I.

The NL delegate considered that the limitation proposed in the reply to question 2.10, namely that any substantial modification can be introduced only on the condition that no other assessment is ongoing, is too restrictive. The NL delegate gave an example of a situation when a substantial modification on Part II could be relevant for one Member State concerned only.

It was suggested to combine questions 2.9 and 2.10 as these are related.

With respect to question 2.11, in order to see whether an application for a substantial modification can be submitted after the end of a clinical trial, COM asked the group to provide examples where this occurred. The group informed that there are a number of examples where substantial modifications could be required after the end of the trial, e.g. in order to keep the trial open to give trial subjects medication for compassionate use (BE), in cases when trial subjects would need to be monitored for a longer time (DE) as well as in certain situations following data analysis. The NL delegate pointed to the fact that the definition of substantial modification does not limit the possibility of introducing a substantial modification after the end of the clinical trial. EMA supported the view that the substantial modification should be allowed after the end of the clinical trial,

COM stated that from a formal point of view it is difficult to substantially modify a process which has already ended. COM asked whether the experts could consider other options to deal with the modifications after the end of the trial. A suggestion put forward by the BE delegate was to give the possibility to re-start a trial through a substantial modification.

The response will be re-drafted.

Due to the limited time left discussion of point 3.b of the cover letter was not held and we moved on to question 3.7 regarding the requirements for the legal representative of a non EEA-sponsor in view of Article 74 of Regulation (EU) No 536/2014. COM asked for the views of the Member States on the proposed response as well as on the proposal of the interpretation put forward by ACRO (document circulated to the group prior to the meeting). The general feedback received from the group was that the legal representative would have to assume the responsibilities for compliance with the sponsor's obligation. The BE delegation pointed to the

difference between the contact person and legal representative. Due to the fact that this is a legal issue the group stated that they would like to consult legal colleagues and their relevant Ministry. Therefore COM asked the members to send feedback in writing on this issue.

COM asked the group to inform whether they would prefer to have a separate guideline on safety reporting. This would include for example:

- CTFG Q&A on RSI
- RSI type, organization and update ; RSI in case of combination (marketed, IMP, AMP)
- Section 7.7.1 from CT3
- Reference to ICH guideline E2F,
- ASR for non-commercial sponsors
- Safety reporting of AMP (marketed and not authorized), alone and in combination with IMPs – SUSARs as well as ASR

The group expressed the wish to include this information in the Q&A document so as to have all information in one place and not as a separate guideline. Therefore COM asked for volunteers to assist with proposing / updating relevant Q&As.

COM asked the group to send comments on the updated document as well as other suggestions for Q&A.

8. Union controls (Art 79 of Clinical Trial Regulation)

COM clarified that the Commission Food Veterinary Office (FVO) will be responsible for conducting the Union controls foreseen in Article 79 of the Regulation. The FVO representative put forward for discussion some preliminary ideas on how the union controls could be organised and performed, in particular as regards the planning and frequency of the controls (both in the Member states and in the third countries), their scope, and participation of the national experts/inspectors from the Member States.

A significant part of the discussion dealt with the participation of national experts in Union controls.

Several delegations (in particular DE and UK) indicated that for them it was not clear what the expectation of the role of national experts is. The delegates stressed that it cannot be assumed that Member States would be prepared/willing to contribute to Union controls. Delegations emphasised that their national inspectorates have a very high workload. The UK delegate asked whether the Commission would pay fees to national experts in exchange for their participation and also questioned the benefit of a Member State in allowing the participation of their experts in Union controls.

FVO clarified that the role of national experts would be mainly to support the Union controls' team with their expertise, apart from the benefit that their participation would offer them in terms of transparency and exchange of good practice. The national experts would not represent their own Member State during Union controls. The national experts would not be responsible for drafting the reports of Union controls. FVO indicated that no fees would be paid to national experts.

COM pointed out that the participation of nationals from one Member State in the assessment of another is current practice for national GMP inspectorates within the Joint Audit Programme. FVO added that this is a practice already carried out in the field of medical devices, on a basis of an explicit provision in the legislation. National experts have participated in audits to third countries in the area of active pharmaceutical ingredients. COM reminded the group that the reports will be made public via the EU portal.

The group pointed to the fact that the Regulation is silent on the participation of the national experts in the Union controls, which is the responsibility of COM.

COM noted that, as previously discussed under point 5 of the agenda, the COM has the intention of including in the Commission Implementing Regulation (on the basis of the working document on GCP inspection) a legal basis for the participation of national experts in Union controls. Nevertheless, the COM agreed that legal clarification could be sought concerning the participation of national experts in Union controls.

UK delegate pointed out that during the negotiations of the Regulation the emphasis of Union controls was more on third countries than on Member States. FVO replied that the Regulation is unequivocal in that both Member States and third countries should be subject to Union controls.

Delegates asked how the Union controls would be organised in practice and what would be methodology of controls. FVO clarified that the details are still to be discussed.

The UK delegate enquired about the proposed pilot exercises, stressing that the Regulation would not yet be applicable. The BE delegate added that it would be necessary to know about the planned pilot exercises earlier.

FVO acknowledged that COM would not start pilots before there was a clear horizon for the application of the Regulation. The pilots (which are in any case subject to the agreement of the Member States concerned) would serve to test the system and assess the degree of readiness to meet the requirements of the Regulation.

The group asked if the reports would contain only observations or also judgements on the performance of the Member State concerned, and whether the reports would contain a sort of gradation of the findings.

FVO replied that since Union controls would be essentially audits, the reports will necessarily contain an assessment as to whether the audit criteria are met or not, therefore they will go beyond the mere statement of observations. Concerning the gradation of findings, FVO stated that there are no particular views one way or the other at this point and that this could be an idea worth considering for further discussion.

The ES delegate stressed that the purpose of Union controls has to be clear and has to support the work carried out by Member States.

Concluding the discussion, COM invited the experts to provide comments on this matter. COM announced that the discussion will continue during the next ad hoc group meeting.

9. Discussion on the involvement of the *ad hoc* group in the preparation of new and revised guidelines on clinical trials (including setting priorities, tentative schedule and responsibilities)

This topic was not discussed due to lack of time. Members are therefore asked to provide comments on the related documents circulated prior to the meeting.

10. Any other business: Labelling issues related to Art 66&67 and Annex VI of the Clinical Trial Regulation, raised by stakeholders *(for discussion)*

COM stated that EFPIA has written to express their concerns on Annex VI of the CTR which makes it mandatory to include certain information such as "period of use" on the immediate and outer packaging of investigational medicinal products. A video prepared by EFPIA on the possible consequences of the implementation of this requirement, such as costs, risk of error, breaking the ATD, waste of products was shown to the group. A common response to queries from EFPIA is required.

COM added that the current provision on labelling of IMPs is covered by Annex 13 of the EU GMP Guide.

The proposal from COM for the revision of the clinical trial Directive reflected the current status. However, during the negotiation of the Clinical Trials Regulation some delegations requested changes, which were agreed by the co-legislators.

Therefore, at this stage where the adoption of the Regulation is very recent and the provisions are not yet applicable, any modification to the annexes would be challenging (its legal possibility would also have to be closely assessed) and they would need to be shared by the co-legislators.

From the discussions, it appears that Annex 13 is currently applied differently in the various MS.

COM invited Member States to send an official position on the three concerns expressed by EFPIA:

- Expiry date on immediate and small packaging
- Replacement of expiry date by electronic system
- Replacement of other information (mentioned in Section D9 of Annex VI of the CTR) by electronic system

If there is a clear official position from Member States, then COM will have to discuss internally how to proceed and to make contact with the European Parliament.

AOB

As there was no AOB the COM concluded the meeting stating that COM is awaiting for comments from delegates regarding:

- both working documents discussed under agenda items 5 and 6
- issues raised during the discussion on the Question and Answer document under agenda item 7, as well as any other suggestions for Q&As as mentioned in these minutes;

- the organisation of union controls discussed under agenda item 8,

After reminding the group that the next meeting of ad hoc group will tentatively be held in March 2015, COM closed the meeting.

List of Participants

Country	Organisation
AT	AGES/BASG
BE	AFMPS-FAGG
BE	CPME - Comité Permanent des Médecins Européens/ EUREC - European research Ethics Committees
CZ	State Institute for Drug Control
DE	Paul-Ehrlich-Institut (PEI)
DE	Federal Ministry of Health
DE	BfArM
DK	Danish Health and Medicines Authority
ES	AEMPS
EE	State Agency of Medicines
FI	Finnish Medicines Agency (FIMEA)
FI	National Committee on Medicinal Research Ethics
FR	ANSM
FR	University hospital of Saint-Etienne
HU	Ethics Committee for Clinical Pharmacology Medical Research Council of Hungary
HU	National Institute for Quality and Organisational Development in Healthcare and Medicines
IE	Irish Medicines Board
IE	The Health Information and Quality Authority
IT	Agenzia Italiana del Farmaco (AIFA)
LI	Amt fur Gesundheid
LT	State Medicines Control Agency
LV	SAM Latvia
NL	Central Committee on Research Involving Human Subjects (CCMO)
NL	Dutch health care inspectorate
PL	The Office for Registration of Medicinal Products
PL	Main Pharmaceutical Inspectorate
PL	Ministry of Health
PT	INFARMED
PT	National Ethics Committee for clinical Research
SI	JAZMP
SK	State Institute for Drug Control
UK	Health Research Authority
UK	Medicines and Healthcare products Regulatory Agency (MHRA)
EMA	EMA