REVISION OF THE 'CLINICAL TRIALS DIRECTIVE 2001/20/EC

EFPIA AND EVM JOINT RESPONSES AND COMMENTS IN RELATION TO CONCEPT PAPER SUBMITTED FOR PUBLIC CONSULTATION

(Reference SANCO/C/8/PB/SF D (2011) 143488)

Executive Summary

- EFPIA agrees that introducing a single submission portal has the potential to remove some of the administrative burden on applicants, provided a number of conditions are met
- However, in order to deliver a significant step forward EFPIA believes that the single submission portal concept should be linked to an optional European assessment procedure for multinational studies
- EFPIA does not agree with the Commission assessment that a central assessment is not appropriate or workable; on the contrary we continue to believe that a fully optional community clinical trial procedure is a valid proposition and that it should be explored further
- To bring a significant improvement over the current situation any new system needs to deliver a number of key objectives. In particular, it should be non bureaucratic, simple and speedy, provide uniformity of conduct of multicenter trials in all concerned Member States, ensure there is consistency between any applicable EU level scientific advice/recommendation and the assessment of the clinical trial, establish a clear and consistent demarcation of tasks between the assessment authorities and the Ethics Committees, and allow the addition of centres in further Member States without triggering a review or a repetition of the assessment carried out in relation to the conduct of the trial in the initial Member States.
- It is not clear that the 'co-ordinated assessment procedure' (CAP), as outlined in the concept paper, is the most appropriate approach to deliver the above mentioned key objectives. .
- We believe that tacit approval timelines should be maintained and Member State adherence improved
- We agree that the requirements for trials within the scope of Clinical Trials Directive should be harmonised, and be more proportionate depending on the risk, type or circumstances of the clinical trials
- EFPIA is supportive of adopting more precise and risk-adapted rules for the content of the application, verification of GMP and for safety reporting
- EFPIA supports further international cooperation in the regulation of clinical trials
- We believe that ideally the measures aimed at delivering key objectives in relation to harmonised and proportionate requirements, and uniformity of conduct of multicenter trials, should be adopted by means of a Regulation.

1. COOPERATION IN ASSESSING AND FOLLOWING UP APPLICATIONS FOR CLINICAL TRIALS.

Single submission with separate assessment

"A single submission would greatly reduce the administrative work of sponsors for submission of documentation to the Member States concerned".

Consultation item no. 1: do you agree with this appraisal? Please comment.

EFPIA and EVM joint response

We agree with the assessment that individual national submission and review procedures have the following consequences:

- largely identical information has to be sent to several different Member States, which creates unnecessary administration
- the requirements set out in the Clinical Trials Directive are applied differently in the different Member States leading to divergent points of view on the same application

- We believe that the single submission portal concept has the **potential to remove some of the administrative burden** of submitting largely identical information to the individual Member States regardless of the assessment procedure that is finally adopted **provided several conditions are met,** in particular, the following:

  1. ***The Clinical Trial Application (CTA) and Ethics Committee (EC) documentation content and format must be fully standardised within the EU and acceptable in all Member States.***

     Sponsors must be able to submit the dossier onto the 'Portal' easily, without any special reformatting. We are concerned that the experience of delivering such e-submission systems within Europe has been fraught with issues, so there would need to be a lot of planning, consultation and piloting before adopting this as the only solution for submitting Clinical Trial applications.

  2. ***Additional national requirements should not be permitted.***

  3. ***For multinational trials*** and where the dossier supporting the application for a clinical trial authorisation is in English, there should be no expectations for additional 'country-specific' documents or translations (either via the central portal or directly to the National

Competent Authorities or Ethics Committees concerned), other than those translations specifically needed for study subjects (e.g. informed consent documents).

4. **The submission portal step must be quick and must not delay the approval/opinion processes.**

   It is not clear if the distribution of the information to the Member States concerned would be using purely an IT solution, or whether there would be the involvement of staff working at the European Medicines Agency which will administer the portal?

   Notwithstanding the manner in which the documents will be distributed **the portal needs to be secure and confidential**
   - Information on the submission only accessible to the sponsor concerned; but accessible to more than one person or groups within each sponsor's establishment and in multiple countries to ensure that there is no delay in submission of data
   - Arrange for Commercially Confidential information (for example the quality sections of the investigational medicinal product dossier) to be accessible only to the National Competent Authorities concerned.

5. Clarification is needed that not only the initial application will be channeled through the EU portal, but also **subsequent amendments**.

6. The Portal approach will require that **sufficient funding** for human resources and infrastructure from EU and/or national level is made available to develop the appropriate submission infrastructure and management. In this regard it is important to keep in mind the fact that the management of differences and complexities requires more time and resources (see below).

- **If the above mentioned issues were appropriately addressed** the single portal approach could facilitate a more product-based approach to CTA assessment, where information submitted for one trial could easily be referred to for subsequent trials in the same or other Member States for the same product (rather than the current, largely protocol-based, approach, where cross-referral is only possible within the same Member State). Such a system would lead to more efficient assessment of multiple clinical trials with the same medicinal product in a development program.

  It could also facilitate maintenance of the Investigational Medicinal Product Dossiers and even potentially make it possible for a sponsor to write a letter of agreement, more easily allowing other sponsors to cross-refer to information already submitted.

- **If the single portal does not address the issue of divergent national requirements (**i.e. requirements above and beyond a "core dossier" of information,) this will not reduce major administrative burdens experienced by applicants outlined below:

Divergent requirements include, but are not limited to:

- Differences in country requirements regarding what documents must go to the EC, CA or both (e.g. ICFs and other patient documents to competent authorities)
- Country specific application forms additional to the Annex I form (and in some cases, different forms for ECs and CAs), web based postings etc
- Differences between countries as to where personal data protection compliance is assessed for the clinical trial application with separate data privacy submissions in some jurisdictions (and different assessment of these requirements)
- Different requirements for import/export licenses when moving product *within the EU* for IMP, non-IMP and trial related materials (e.g. biological samples such as blood)
- Different interpretations of what constitutes a substantial amendment
- Lack of clarity around fees for submissions , amendments and annual fees for CTAs
- Requirements in some countries for Sponsor to send EC approvals to the CA

Information on manpower, costs, administrative burden

- Divergent interpretation of the 'Directive' in national legislation complicates and increases the need for active tracking of requirements across and within the Member States by staff of pharmaceutical companies.
- Resources required to translate local language Member State requirements and further interpret what is intended
- Resources needed for resubmission discussions to clarify Member State requirements

- Although standardisation of format and content is key, it will be equally important that the future harmonised CTA and EC dossiers do not consist of a cumulative list of all possible national requirements. They **should reflect the 'core' requirements** in current European Commission guidelines, i.e. those which can be scientifically and ethically justified and are required by a majority of the Member States. We suggest that the future *standardised* CTA and EC requirements should be subject to a **transparent public consultation**.

- **However submission through a single EU portal even if successful would not address one of the major issues negatively affecting our later stage trials (Phase IIb trials onwards), that of multiple and divergent assessments of clinical trials.**

Single submission with separate assessment

"A separate assessment would insufficiently address the issue set out above: The difficulties created by independent assessments would remain".

Consultation item no. 2: Do you agree with this appraisal? Please comment.

EFPIA and EVM joint response

Yes, as clearly identified in responses to the Commission's previous consultation on the functioning of the Clinical Trials Directive, separate assessments by Member States significantly contribute to the current shortcomings of the Directive.

It seems inevitable that Member States would still have a different focus in their review procedures and therefore separate national assessment would continue to result in different review questions being raised and at times in requests for specific local protocol amendments to be made.

Therefore, for true benefit, the single submission portal concept should be linked to an **optional European assessment procedure for multinational studies**.

If there is no option for a single or coordinated assessment, and if country-specific requirements remain, the drawbacks of a single portal will outweigh any enhanced convenience of a unique submission portal. For example,

1. country-specific documents (including translations) would be rate-limiting for submitting a complete file in Europe;
2. the additional administrative step of passing via a single portal might actually delay start of the national approval procedures;
3. any issues raised during national assessments would presumably have to be addressed directly with the concerned national authority anyway rather than via the single portal. Having to address the issues via the portal would just add another administrative layer. By the same token it is not clear how amendments could be managed via a central portal should the outcome of national reviews result in different conclusions and recommendations.

All these independent national assessments are an impediment to carrying out Clinical Research in the EU, especially for large multi-country studies.

For the future system to bring a significant improvement over the current situation it must:

- Be non-bureaucratic
- The clinical authorisation procedure(s) must be simple and speedy
- Provide uniformity of conduct of multicenter trials in all concerned Member States
- Ensure there is consistency between EU level scientific advice/recommendations where applicable (CHMP, PDCO, CAT, PRAC) and the assessment of the clinical trial
- Establish a clear and consistent demarcation of tasks between the assessment authorities and the Ethics Committees (it is even more important if and to the extent that it is considered that "ethical issues fall within the ambit of Member States" thereby suggesting that such matters may, at least to some extent, be assessed differently in different countries)
- Allow the addition of centers in further Member States without triggering a review or a repetition of the assessment carried out in relation to the conduct of the trial in the initial Member States.

Finally it is worth noting that differing national requirements and assessments may impact the ability of a patient to participate in a trial, or not, depending on the country or region where he/she lives.

Single submission with subsequent central assessment

"A central assessment is not appropriate for clinical trials approval and would, as regards clinical trials, not be workable in practice for the following reasons:

- *This option would insufficiently take account of ethical, national, and local perspectives. For these aspects, a parallel, national, procedure would have to be established in any case.*
- *The sheer number of multinational clinical trials per year (approx. 1 200) would make centralised assessment very difficult. To this would add all substantial amendments of the clinical trials.*
- *The involvement of all Member State is not needed, as very few clinical trials are rolled out in more than five or six Member States.*

Moreover, a Committee structure requires frequent meetings with a robust supporting infrastructure. The costs (and, consequently, fees) involved would make this mechanism unattractive for academic researchers."

Consultation item no.3: Do you agree with this appraisal? Please comment.

EFPIA and EVM joint response

No, we do not think that a centralised approach is necessarily inappropriate.

Although we agree with the Commission that the proposal for a central assessment of clinical trial authorisations for all clinical trials by a Committee similar in size and structure to that set up for reviewing applications for marketing authorisations could make this approach unworkable, costly and ultimately unattractive, EFPIA **continues to believe that a fully optional community clinical trial procedure** as outlined in previous consultations (i.e. a single CTA dossier submitted centrally, reviewed once and resulting in the granting of a Community Clinical Trial Authorisation) **is a valid proposition**.

Optionality and work load.

- If an optional centralised assessment procedure was available, sponsors would most likely choose to use it for clinical trials involving more than 2 or 3 Member States (MSs) and statistics have shown that the number of these trials is modest in comparison with the number of single Member State trials but usually involve a much larger number of patients.

- It would avoid the current duplication of CTA assessments and the well over one hundred 'country specific requirements' that do not add to patients' protection or the quality of a trial
- Resources within the NCAs would be saved as there would not be multiple assessments of the same data;

Assessment

- The mechanism for delivering a centralised assessment would not necessarily have to be similar to the centralised marketing authorisation procedure.
- The sponsor would submit an application to the single EU portal administered by the EMA mentioned in paragraph 1.1 of the Concept Paper and a high level administrative validation aimed at checking that the application contains the expected documents and particulars would be performed.
- The application would be "distributed" to a virtual assessment team including CTA assessors and as appropriate relevant experts (e.g. paediatricians, toxicologist, expert in biotech, CMC, gene or cell therapy products, biostatistics, etc) drawn from across the Member States. The person leading/coordinating the virtual assessment/making sure timelines for a given project are complied with could also be drawn from a national agency. This person would be clearly identified as such both to the other evaluators and to the applicant
- We do not believe that a Committee similar to the CHMP would need to be set up. New types of committees have been set up. In relation to medicinal products for human use the legislator has recently created the 'Pharmacovigilance Risk Assessment Committee' or PRAC. The role of this Committee is extremely important and it will heavily rely on the work carried out by national agencies' experts including on assessments resulting from worksharing activities (e.g. assessment of Periodic Safety Update Reports or PSURs for medicinal products authorised in accordance with national procedures, MRP and DCP). The flexibility built into the organisation of this new committee is forward looking.
- Use of new working methods (e.g. WebEx) should also be considered.
- A centralised assessment approach would facilitate access to the widest pool of (regulator) expertise across the EU, which is particularly important for advanced therapies, rare diseases, and/or innovative or complex study designs *(e.g.*, complex adaptive design).
- Under a centralised system it would be easier to streamline and perform sequential assessment of different studies within a clinical program for a new medicine.
- A central assessment would clearly resolve the issues of multiple and divergent assessment of clinical trials and contribute to efficient and competitive clinical research in Europe.

Ethical, national and local perspectives

We fully understand that some ethical matters may require that local perspectives be taken into account (e.g. in relation to insurance and indemnity, recruitment, reward, suitability of investigators and clinical sites, the ethics of some therapies derived e.g. from stem cells, etc.) However it is not clear what grounds may justify divergence between Member States in relation to the ethical assessment of clinical study protocols and the core information submitted to obtain informed consent. We believe that ethical standards which form part of Good Clinical Practices could be assessed at the European level.

The principles outlined in the declaration of Helsinki are applicable in the EEA and the "Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biological and Medicines: Convention on Human Rights and Biomedicines" could form the basis for the assessment of ethical aspects of clinical trials.

EFPIA's response to consultation item no. 2 outlines several key criteria which the clinical trial authorisation system will need to meet to bring a significant improvement over the current situation.

A centralised assessment resulting in an authorisation valid throughout the EEA would also make extension of a clinical trial to further Member States easier. There are many different reasons why such extensions may be needed: this can be the case for example when the target patient population is very small, when many trials in the same populations are underway at the same time, etc. The concept of a single authorisation valid across the EEA would have a substantial impact towards improving the competitiveness of the EU as a region to conduct clinical trials.

Single submission with a subsequent 'coordinated assessment procedure'

"… the three areas which are considered in a clinical trials application:

a) The risk-benefit assessment, as well as aspects related to quality of the medicines and their labeling…
b) Ethical aspects related to informed consent, recruitment and reward…
c) Local aspects related to suitability of sites, the investigator and national rules…"

Only the aspects under point a) would be suitable for the CAP. In particular, the aspects under b) and c) are not suitable for the CAP as the relate to ethical issues (as is the case for b) or to local expertise (as is the case for c)"

Consultation item no.4: Is the above catalogue complete?

Consultation item no. 5: do you agree to include the aspects under a) and only these aspects, in the scope of the CAP?

EFPIA and EVM joint response

1) General consideration on the 'coordinated assessment procedure' (CAP) option outlined in this section

As indicated in EFPIA's response to consultation item no. 2 for any future system to be a significant improvement over the current situation it should be non bureaucratic, simple and speedy, provide uniformity of conduct of multicenter trials in all concerned Member States, ensure there is consistency between any applicable EU level scientific advice/recommendation and the assessment of the clinical trial, establish a clear and consistent demarcation of tasks between the assessment authorities and the Ethics Committees, and allow the addition of centres in further Member States without triggering a review or a repetition of the assessment carried out in relation to the conduct of the trial in the initial Member States.

In the absence of a fully centralised procedure a CAP must be able to deliver these key objectives. However as set out in our responses to consultation items no 2 and 3, it is not clear that the coordinated assessment procedure as outlined in the Concept Paper is the most appropriate approach to deliver these key objectives.

- ***Reporting Member State***

The operation of the proposed coordinated assessment procedure will rely heavily on the project management skills, capacity and resources of the 'Reporting Member State'. It will also rely on the ability and willingness of all concerned Member States to strictly comply with the mandated review timetable. The responsibilities and powers of the 'Reporting Member State' would need to be clearly defined, as would the proposed process for deciding the Reporting Member State.

- ***Role for the EMA***

It is not clear if it is proposed that the EMA acts as secretariat, monitors compliance with procedural timelines, and helps resolve issues if they were to arise. We think there could be a role for the EMA.

- ***Single decision per Member State***

The concept paper indicates that the CAP would lead to a 'single decision' per Member State including the scientific and ethical / local aspects of the trial.
Clarification would be welcomed on the definition of "single decision per Member State" where authorisations/ clearances from a number of committees may be needed before a trial can start in particular when the sponsor intends to conduct the trial in several centres in a given Member States. Strict timelines for issuing of the national CTA approval following completion of the coordinated scientific review would have to be mandated and clarification would be welcomed on the proposed process for ensuring that the "single decision per Member State" is made and communicated to study sponsors in a timely manner (i.e. no more than 60 days from a complete dossier submission with completeness being defined as outlined in our response to consultation item no 1 to the central portal to communication of single decision per Member State).

- ***It is proposed that the CAP only address certain aspects of the assessment of an application*** for a clinical trial.

We are concerned that the proposed CAP has a fairly restricted scope and finally leaves it to Member States to make a decision on all aspects of the trials thereby allowing for differing decisions to be taken. The uncertainty of differing decisions and timings per Member State would undermine any benefits that might be gained from the CAP and would continue to affect the competitiveness of the EU as a place for clinical research.

Should a sponsor wish to add centres in other MSs (for example as a result of the recruitment in the Member States concerned by the CAP being more difficult/slower than expected) it is not clear how this sponsor would have to proceed. Repeat the CAP?

2) <u>Response to consultation item no. 4</u>

It is somewhat unclear whether the phrase 'above catalogue' refers to the list of areas/items to be considered in a clinical trials application in general or the list of items under paragraph a)

which corresponds to the aspects which the authors of the concept paper suggest would be suitable for the CAP.

The "catalogue" of areas/items to be considered in a clinical trials application appears to be complete. However,

- the concept of 'normal clinical practice' may be interpreted very differently in different Member States.
- the catalogue should not be augmented to allow for specific national requirements to be included in relation to the "risk-benefit assessment" and the quality and labeling of the medicines referred to under paragraph (a) , nor in relation to the ethical aspects related to informed consent mentioned in paragraph (b).

3) Response to consultation item no. 5

The aspects which are proposed to be included in the assessment procedure are in general appropriate. However it will be essential that the remit of the Ethics Committees review is clearly and explicitly defined across Europe. This is currently not the case. Overlaps between regulatory assessments and national EC reviews increasingly create problems and will be particularly obstructive to the functioning of the CAP. They must be eliminated or at least minimised.

The regulatory approval and ethical "single opinion per Member State" must be granted in parallel and be mutually independent. This is currently not the case in all Member States where for instance a competent authority approval may be dependent on a prior positive EC opinion. Unless the revised EU legislation specifies mutual independency, the CAP process will be obstructed. However independency is not synonymous with 'no communication' and communication channels should be encouraged.

Mechanisms should be explored for improving cooperation and exchange of best practices cooperation (e.g. cooperation platform) between Ethics Committees across the EU.

Resolving disagreement amongst Member States

The concept paper proposes three approaches for resolving disagreement amongst Member States about the assessment as follows:

(1) an individual Member State could be allowed an 'opt out', if justified on the basis of a 'serious risk to public health or safety of the participant'; or

(2) the Member States concerned could vote on the issue and decide by simple majority; or

(3) the matter could be referred to the Commission or the Agency for a decision at EU level.

Consultation item no.6: Which of these approaches is preferable? Please give your reasons.

EFPIA and EVM joint response

The first approach (an individual Member State could be allowed to 'opt out') is in general preferred for the following reasons:

- Considering that the introduction of this option is to improve efficiencies in how multinational trials are conducted, the best option would be one that ensures no delay to study start in the countries included. The criteria for opting out should however be reconsidered (see "additional considerations" below). It is suggested the wording could be adjusted to also allow sponsors to remove countries, as appropriate.
- If the decision were to be made by simple majority, this would seem to 'force' member states to accept the conduct of a trial in their country, which they would not have approved if the national procedure was followed. The legal basis for this under a Directive is unclear.

  A referral to the Commission or the Agency is likely to delay the procedure.

Additional considerations on the various options

First approach

This option would allow Member States to "opt out" of the process, which would allow the procedure to continue to conclusion for the other Member States.

It would not be an "all or nothing" approach. Although it is hard to imagine that a trial/IMP would entail a 'serious risk to public health' or safety in one Member State exclusively, this ground has frequently been put forward as a motive to refuse to recognise a marketing authorisation granted in other Member States. This has contributed to the adoption of a strict definition of 'serious risk to public health' in relation to applications for marketing authorisation; and in the centralised procedure being increasingly preferred by applicants for applying for a marketing authorisation for a new medicinal product. Given the restricted number of patients exposed to treatment and the controls in place during clinical trials it would seem more appropriate to limit the criterion for opting out to a "probable serious risk to the safety of the participant" based on local or national specificities such as medical practice.

Second approach

This option may encourage consensus building and use of simple majority allows for open discussion among the Member States regarding what is considered a serious risk to public health. However any votes would have to be conducted within the overall standard CTA timeframe and it is not clear how this could be ensured. It is also an "all or nothing" approach, preventing the CTA going ahead in Member States which would have approved the CTA. This is not a concern if EFPIA's proposal for a single review and approval system is adopted. However, we have concerns about using an all or nothing approach under the Commission's CAP proposal, where Member States retain the right to make a national decision on CTAs. An alternative possibility is a combination of 2 and 1 (vote by simple majority with a possibility to withdraw the application in a Member State(s) which does not agree to support the proposed study) may be considered.

It is not clear whether the proposed way forward would imply that a Member State with a large population that could be impacted by a trial will have no more influence on the approval of a CTA than a smaller Member State with a smaller population.

Third approach

This approach would resolve disagreements between Member States but could impact timelines considerably. It is also an "all or nothing" approach, preventing the CTA going ahead in Member States which would have approved the CTA. It is also unclear based on which criteria or input the EMA or Commission would arbitrate the disagreement (especially in the absence of a central assessment body the issue(s) could be referred to). A combination of approach 2 and 3 (where the number of Member States involved in the CAP is even and no simple majority can be reached) may be suggested however the timeline issue is still a concern and the benefit in terms of harmonised outcome is unclear, since in the end Member States will adopt separate single opinions.

Mandatory or optional use of the Coordinated Assessment procedure

The CAP could be mandatory for **all** clinical trials **or all multinational** trials **or completely optional.**

Consultation item no.7: which of these approaches is preferable

EFPIA and EVM joint response

Should the CAP finally be the agreed way (but see our response to consultation item 3) it should be completely optional to allow the maximum flexibility (e.g. if the sponsor only wants to include 2 or 3 countries).

The CAP cannot be applied to single country trials and therefore the CAP cannot be mandatory for all clinical trials (this is not a valid option).

It is also worth noting that some Member States have implemented streamlined CTA procedures for phase I studies, many of which take place at only one Member State, and sponsors should not be denied the option to utilise these procedures.

Tacit approval and timelines

It is proposed that the CAP be based on the concept of an obligatory single authorisation per Member State prior to the commencement of the clinical trials, that the timelines should not be longer than 60 days 'as a general rule', and that the timelines could be shortened for so called 'type-A trials' which could be identified as such "in a pre-assessment" on the basis of several criteria.

Consultation item no.8: Do you think such a pre-assessment is workable in practice? Please comment.

EFPIA and EVM joint response

The introduction of a streamlined assessment process/shorter timelines for "low risk" clinical trials is in principle welcome. The recent adoption of a competent authority notification process for clinical trials in the UK for marketed medicines being used in their authorised indication is a good illustration of how such a proposal could be implemented across all Member States. However it is difficult to assess the workability of the current proposal across the whole EEA and the approach outlined in section 1.3.4 of the concept paper raises a number of comments and concerns.

- **Tacit approval and timelines**

We challenge the notion that tacit approval should be abandoned simply because it is rarely applied. Tacit approval should have been applied in accordance with the Clinical Trials Directive, but some Member States' lack of adherence to the Directive's timelines has had the result that sponsors are effectively obliged to await a written response before commencing a trial, even where the 60 days have elapsed. The introduction of a coordinated or Community procedure could present an opportunity to better enforce adherence to timelines, as these will be more transparent to the EMA and Commission, and, therefore, for tacit approval to be applied.

The 60-day approval period is interpreted differently in different Member States (e.g. validation periods, clock-stops etc). The revised legislation should stipulate that the total possible review period is expressed in calendar days from reception of a complete application (i.e. application containing the documents and particulars mandated in the EU legislation) to decision.

If clear timelines for review are being given, then it should be ensured that Member States are following the timelines.

The implementation of a revised procedure for clinical trial approval would provide an opportunity to consider shortening the timeline thereby making the European procedure more attractive for international sponsors. We suggest that the objective should be to complete the assessment procedure in significantly less than 60 days. Several Member States, e.g. UK, Ireland, Germany, Denmark, Austria and Belgium, have implemented timelines of 28-to 35 days.

The management of amendments is critically important and lack of compliance with deadlines in relation to the approval of amendments has a serious impact on the conduct of trials, especially in the case of multicenter trials. Shorter timelines should be considered (e.g. 10 days for assessment and 5 days for authorisation of an amendment under a coordinated assessment or Community procedure).

Instead of a general approval timeline for all different types of trials, we are proposing inclusion of more detailed timelines that Member States should follow, e.g. a 30-day tacit approval timeline for studies that have already undergone some prior competent authority assessment, e.g. studies agreed in the context of a Scientific Advice, or which are part of an EMA-PDCO agreed Paediatric Investigational Plan.

Consideration should also be given to providing for shorter timelines when it is proposed to perform a clinical trial concerning a medicinal product which is not authorised in the EU but has been authorised based on a dossier meeting international standards (e.g. authorised in an ICH region).

- **Concept of pre-assessment**

There are doubts that a pre-assessment will necessarily result in an actual benefit in terms of review time. The pre-assessment will constitute an administrative burden and may even result in longer assessment timelines (e.g. when the outcome of the pre-assessment is that the clinical trial does not qualify as a "Type-A" trial). Therefore we believe that pre-assessment in relation to qualification as a "Type- A trial" must not be mandated.

We propose that the following approach is adopted:

- "Type A" trials should be defined as clearly as possible (see comments on currently proposed definition below).

- The sponsor will assess whether the study it intends to undertake qualifies as a Type-A trial against the criteria clearly outlined in the legislation and submit the corresponding clinical trial application in accordance with the Type-A procedure. The application will contain the rationale based on which the sponsor has determined that the clinical trial met the definition of a Type-A trial.

- Should the sponsor consider that the clinical trial may qualify as Type-A trial but prefer to check whether its assessment is correct it will have the possibility to ask for an advice

- The documentation supporting the application for advice should be strictly restricted to those aspects of the trial that are directly relevant to definition as "Type A"
- The pre-assessment could occur at any time prior to the submission of the CTA
- The process is rapid

- **Criteria for meeting the definition of "Type-A" trial**

The vast majority of interventional trials do not fulfil criteria (a) and for those that do, then gaining consensus on criteria (b) as they are currently defined may be too variable to be of use.

Even the definition of "*part of a standard treatment in a Member State concerned*" is somewhat unclear. What happens if the investigational product is accepted as "standard treatment" in one member-state, but not in another?

The definition of "*interventions in the trial do not pose more than insignificant additional risk to the safety of the trial subject compared to normal clinical practice*" could be made clearer.

It may be difficult to give a clear definition of what constitutes an "*insignificant risk*". Additionally, the notion of "*normal clinical practice"* may also vary considerably among Member States.

The criteria for a "Type-A" trial should be sufficiently broad to streamline the current procedures while safeguarding patient safety.

We suggest that these criteria are discussed with all stakeholders (e.g. in (a) workshop(s))

As mentioned earlier in relation to other proposals for improving the regulatory environment for clinical trials in Europe, consistent interpretation of the definition of a Type A trial and a high level of commitment across all Member States is necessary to ensure that this particular proposal delivers its intended objective.

It is not clear whether in the case of a CAP a multicenter- multi Member States type A trial could automatically be extended as such (i.e. without any re-assessment /confirmation that the type A status is confirmed) to include a site located in an additional Member State (e.g. tell and do 15-day procedure).

As previously mentioned (in particular in our comments on consultation item 3) we envisage an optional EU procedure involving a single assessment of the CTA on the behalf of the whole EU. Approval of the CTA following a single assessment would allow the trial to be conducted anywhere with the EU (subject to opinions from relevant ethics committees) without the need for a further authorisation from the NCA in the Member State concerned.

2 BETTER ADAPTATION TO PRACTICAL REQUIREMENTS AND A MORE HARMONISED RISK ADAPTED APPROACH TO THE PROCEDURAL ASPECTS OF CLINICAL TRIALS

Limiting the scope of the Clinical Trials Directive

Enlarging the definition of 'non-interventional trials'

"*Rather than limiting the scope of the Clinical Trials Directive through a wide definition of 'non-interventional trial', it would be better to come up with harmonised and proportionate requirements which could apply to all clinical trials falling within the scope of the present Clinical Trials Directive."*

Consultation item no.9: Do you agree with this appraisal? Please comment

EFPIA and EVM joint response

This section of the Concept Paper is a little difficult to follow.

Our interpretation is that the following is proposed:

- to keep the current distinction between interventional and non interventional trials and abstain from broadening the scope of the definition of non-interventional trials
- to keep the scope of the Clinical Trials Directive as it is.

As such we agree that the requirements for trials within the scope of the Clinical Trials Directive should be harmonised and more proportionate depending on the risk, type or circumstances of the clinical trials.

However, the acceptability of the proposal (in particular not to broaden the definition of non interventional trials) is absolutely reliant on the "proportionate requirements" for clinical trials being reasonable and practical.

A decision tree for determining if a clinical study is a clinical trial under the 'Clinical Trials Directive' is provided in the Annex to the Questions and Answers document included in EudraLex Vol 10. We note that this decision tree puts a broader range of clinical studies outside the scope of the Directive than just non-interventional trials as described in the Concept Paper.

A particularly important type of clinical study is the exploratory medicine method development study in which medicinal products, known to produce receptor occupancy, biological,

pharmacological or other effects, are used to develop clinical methodologies that improve the detection, measurement or evaluation of those effects. These kinds of studies are critical for the improvement of exploratory medical sciences and it is important that their conduct in the commercial and non-commercial setting remains unhindered by unnecessary regulation. It is paramount that broadening the scope of the Clinical Trials Directive to include these studies raises no additional hurdles to their conduct

"Proportionality" in requirements has to mean that the requirements are not the same for all the trials within the scope of the Directive and that some requirements are not applicable to some trials at all. This must be formally acknowledged in the Directive and an annex to the basic legal act will have to contain appropriate information in this regard (clear definitions of types of trials in terms of level or risk, (non) relevance of requirements in relation to the level or risk and /or some situations, possibility of shortened timelines and possibility of notification as opposed to applications for clinical trial authorisation, etc).

Comments on non-interventional trials as they are defined in the Clinical trials Directive

We are of the opinion that the Directive should continue not to apply to "non-interventional trials" because their pla²ce is **not** in this legislation and their inclusion into scope of the Clinical Trials Directive would greatly increase the administrative burden to sponsors without any public health justification.

It is worth noting that the principles of the Declaration of Helsinki are applicable to all non interventional trials.

The new Pharmacovigilance Legislation (Directive 2010/84/EU) lays down provisions for non-interventional post-authorisation safety studies (they are reviewed by the PRAC and the endorsed protocol is simply forwarded to the competent authorities of the Member States where the study is planned to be conducted suffices to commence the study). Should it prove desirable in the future to harmonise certain aspects of other non-interventional trials (i.e. non interventional trials other than the post authorisation safety studies) this should be done in completely separate legislation after very careful consideration and at a later stage.

Limiting the scope of the Clinical Trials Directive

> *Excluding clinical trials by 'academic/non-commercial sponsors' from the scope of the Clinical Trials Directive.*

"Rather than limiting the scope of the Clinical Trials Directive, it would be better to come up with harmonised and proportionate requirements for clinical trials. The proportionate requirements would apply independently of the nature of the sponsor ('commercial' or academic/non-commercial')."

Consultation item no.10: Do you agree with this appraisal? Please comment.

EFPIA and EVM joint response

The nature/stringency of the requirements and obligations should not be driven by the status/identity of the sponsor and the assessment of the potential benefit- risk and ethical aspects of a trial should be based on the same harmonised and proportionate requirements.

We do recognise that some sponsors find difficulty in complying with the legislative requirements. We also recognise that this can have an impact on the ability for those sponsors to conduct clinical research in the EU.

We believe that those provisions of the legislation that cause difficulty for 'academic' sponsors should be identified and reviewed. The impact of these provisions on the safety of trial participants should be considered. If, by excluding these provisions, there is no impact on the safety of clinical trial participants, the reasons for including those provisions in the clinical trial legislation and applying them to all sponsors need to be re-considered.

This approach would then remove those elements of the legislation that are problematic for 'academic'/non-commercial sponsors while maintaining the high standards of patient safety and ensuring consistency in application of the EU legislation across all clinical trials' sponsors regardless of who the sponsor is.

More precise and risk-adapted rules for the content of the application dossier and for safety reporting

"This approach would help to simplify, clarify, and streamline the rules for conducting clinical trials in the EU by providing one single, EU-wide, risk-adapted set of rules."

Consultation item no.11: Do you agree with this appraisal? Please comment.

Consultation item no. 12: Are there other key aspects on which more detailed rules are needed.

EFPIA and EVM joint responses

Response to the question raised in Consultation Item no. 11

EFPIA is supportive of adopting more precise and risk-adapted rules for the content of the application and for safety reporting. However we believe that there needs to be a greater awareness, experience sharing, discussion with all stakeholders and understanding of what constitutes risk-based approaches in relation to dossier content, trial management and the regulatory oversight of clinical trials.

For example the following need to be considered:

- what specific criteria are to be considered (e.g. to define risk to trial subject safety, risk to data reliability and robustness)? The addition of examples would help better understanding these concepts.
- how would the risk adapted rules be applied in practice
- any link to GCP activities?

In order to be effective, annexes to the basic legal act must remain focused on dossier and reporting requirements and not be too prescriptive in content, i.e. they must be able to support an effective science based decision on any particular protocol. Yet they must also be sufficient clear and understandable to ensure that they are consistently interpreted and implemented throughout the EEA. This is challenging given the (1) differences in normal clinical practice across Member States (a clear EU definition of the term "normal clinical practice" will need to be agreed), (2) the varying cultural attitudes towards risk within the Union, and (3) the impact of the lack of implementation or inconsistent implementation of EU Directives. Another challenge is that while annexes to the basic legal act will better ensure consistency in the rules applicable across Member States which is a must, they will need to be updated from time to time through delegated acts and these revisions take time.

We note that the European Commission proposes to base the content of the above mentioned annexes on the latest version of Commission guidelines (CT-1, CT-2 and CT-3). It should be carefully considered whether the principles set out in these documents are suitable for inclusion in the annexes and all stakeholders should be extensively consulted while drawing up the annexes of risk-adapted rules.

- **With regards to divergent interpretation on data requirements**, these relate particularly to inconsistency in the documentation required by the different NCAs in order to assess CTAs. These mostly relate to the Quality data package, both in terms of the documentation format and sometimes the substantive data content, supplied in relation to investigational medicinal products (IMPs) used in the study (test drug, comparator(s) and placebo).

  However, rather than there being very many differences in the actual documents required between the Member States for the CTA, the more serious concern is the individual NCA expectations on the actual data content for some of the EU common documents, e.g., differences in the NCA interpretations of how certain question in the EU Annex 1 should be answered, and differences in the interpretation of some of the Directive's definitions (e.g., Sponsor, Applicant, Legal Representative etc).

  Some Member States also demand that the updated documents being supplied in a substantial amendment package must have not only a summary of changes (standard practice), but also a "track changes" version as well as a clean version.

  The NCAs also have different levels of translation requirements, e.g., some will accept a CTA fully in English, whilst others require various documents be translated for submission.

- **Safety reporting rules** need to be streamlined across Europe. Quality rather than quantity is the main objective, i.e. the information obtained from safety reporting in clinical trials is useful and meaningful. It needs to be comprehensive enough such that, following analysis, a thorough understanding of the safety profile of the products and procedures used in the trial is available

  Expedited safety reporting should be to Eudravigilance only with no duplicate reporting to national authorities. Expedited and periodic safety reporting to ethics committees and investigators is of doubtful value and responsibility for the safety assessment should rest with the sponsor and competent authorities. Therefore, we propose that there is no obligation to report expedited or periodic safety reports to the ethics committees (who do not have resource or expertise to deal with these reports) or investigators (who should receive safety updates via the updates to the Investigators Brochure). In relation to reporting to ethics and investigators, if this is to be continued, more detailed rules are needed as to which reports are required and the timescales involved for these submissions. For example we suggest that

aggregate reports be sent to Ethics Committees (i.e. executive summaries of Development Safety Update Reports (DSURs)[1]).

All the above mentioned difficulties add to the administrative complexity and burden of conducting multi-country clinical trials in the EU, and would not seem to be essential to the protection of patients, public health or data quality. These issues must be addressed to improve and simplify the clinical trial application process and the conduct of the trials in Europe.

EFPIA response to the question raised in Consultation item no.12

Any new/revised legal instrument should set out a range of detailed procedures and provide clearer definition (e.g. for IMP, legal representative, reporting procedures).

The classification of amendments as substantial or non-substantial should be further harmonized. The current guideline is not clear enough to prevent Member States from adopting different approaches for example in relation to the addition of study sites, annual updates of the Investigator's Brochure where the changes are not substantial, etc. Appropriate clarifications should be provided.

[1] For further detail on the content of the executive summary in DSURs, see beginning of section of ICH E2F guideline accessible on the EMA website using the following link:
http://www.ema.europa.eu/ema/pages/includes/document/open_document.jsp?webContentId=WC500097061

Clarifying the definition of 'investigational medicinal product' and establishing rules for 'auxiliary medicinal products'

A cumulative approach is proposed to address the issues resulting from legal uncertainties surrounding various aspects in relation to above matters

"This combined approach would help to simplify, clarify and streamline the rules for medicinal products used in the context of a clinical trial".

Consultation item no. 13: Do you agree with this appraisal? Please comment.

EFPIA and EVM joint response

We largely agree with the proposal outlined in the Concept Paper, in particular a narrowed definition of investigational medicinal product would be welcomed. We also agree about the uncertainties of classification of non-investigational medicinal products (nIMPs) and the need for establishing clear and proportionate requirements. However the creation of the term "auxiliary medicinal product" raises the question - does the term auxiliary medicinal product replace the term nIMP or is it a term that is intended to be used as well as nIMP? Having an additional category of products used in clinical trials increases complexity and the opportunity for confusion. It is essential therefore that there is a high degree of clarity regarding what products fall within the definition of "Auxiliary Medicinal Product".

We strongly believe that add-on therapies and background therapies given to all patients as well as ancillary materials such as infusion/saline solutions etc. should explicitly be categorised as 'auxiliary medicinal products'. PET tracers used as a diagnostic agents and other diagnostics should also be included in the list of auxiliary medicinal products.

The acceptability of this proposal is absolutely reliant on the requirements for "Auxiliary Medicinal Products" being reasonable, practical and proportionate to the risk related to their use in the trial. For example the requirements for product supplied by the sponsor and products that patients receive from commercial sources, in which case only the rules for marketed products should apply. Also critical for this proposal's acceptability is a **consistent application** of the requirements **across all Member States.**

Insurance/indemnisation

Two policy options are proposed for addressing the identified issue:

- "Removing insurance/indemnisation requirements for low risk trials"
- "Optional indemnisation by Member State"

"Both policy options could be a viable solution"

Consultation item 14: Which policy option is favourable in view of legal and practical obstacles? What other options could be considered?

EFPIA and EVM joint response

We do not consider the options suggested in the Concept Paper to be appropriate to address the above mentioned issues for the following reasons:

Notwithstanding the fact that we believe that insurance requirements should be maintained for all trials the first option raises the following comments: risk characterisation of a Clinical Trial remains a difficult exercise, and therefore may reduce the impact of the first proposal (removing insurance/indemnisation for low-risks trials). Furthermore the insurance issues for the other trials, not considered as low-risks, will not be solved, unless other measures are taken.

The second proposal (optional indemnisation by Member State : obligation for Member States to provide for an indemnisation of damages incurred during clinical trials performed in their territory, taking into account the national legal system for liability) may not contribute towards addressing the lack of harmonization and may not lead to a consistent approach between the different Member States. A lack of transparency will certainly remain, for insurance policy terms and conditions as well as loss history. It could also have a side effect of relocating the trials, not taking into consideration the needs of the study, but the policy terms and conditions available locally.

Other possible ways forward could be explored, for example the establishment of an EU Clinical Trials Policy that would set up a general minimum insurance limit and would be deemed acceptable to all ethics committees.

Single sponsor

Two options are proposed as follows:

- "Option 1: maintaining the concept of a single sponsor
- Option 2: allowing for ac concept of 'multiple sponsorship'/joint sponsorship'/shared sponsorship'/'co-sponsorship', where each sponsor is 'responsible' for a specific task or for the conduct of the trail in a Member State"

"In view of the above, option 1 may be preferable provided that:

- *It is clarified that the 'responsibility' of the sponsor is without prejudice to the (national rules for liability; and*
- *It is ensured that the regulatory framework for clinical trials in the EU is truly harmonised"*

Consultation item no. 15: Do you agree with this appraisal? Please comment.

EFPIA and EVM joint response

EFPIA agrees that the concept of single sponsor should be maintained because we believe it is best suited to ensure clear assignment of roles and responsibilities while multiple/joint sponsorship would increase complexity and could result in uncertainties in responsibility.

However the one sponsor approach should be supported by more emphasis /directions regarding the sharing or delegation of tasks/functions by the sponsor to an individual, company, institution or organisation.

For example, the Questions and Answers document included in Volume 10 of the Rules governing medicinal products in the European Union states: "A number of parties may agree, in writing, to form an organisation according to Article 2 of Directive 2001/20/EC and to distribute the sponsors tasks/duties and functions between different person(s) and/or organisation(s). This is done in such a way that the collective agreement fulfils all the required roles and responsibilities of the sponsor". These types of arrangements need to be explicitly encouraged and facilitated as they are necessary to support the work of collaborative groups, including public-private partnership projects (such as IMI, for example), which include multiple stakeholders.

Additional comments:

- The concept paper notes that the concept of responsibility for a trial is often confused with liability vis à vis the trial subject in case of damage where liability is a matter of civil/common law regarding contractual or extra contractual obligations (i.e. national rules apply). For reasons of transparency of sponsors becoming active in the EU it may be of added value if the EMA or the Commission or the Member States under the HMA prepared an exhaustive overview of implemented provisions concerning responsibilities and liability rules of all Member States affecting sponsors and made this overview publicly available.

- Clarifying some definitions (e.g. sponsor, applicant, legal representatives) which are interpreted differently in different Member States may also contribute to better understanding of the concept of responsibility and the possibility to share or delegate tasks and responsibilities.

Emergency clinical trials

The Clinical Trials Directive could be amended to the effect that the informed consent and the information from the investigator may take place during or after the clinical trial under (conditions listed in the Concept Paper submitted for public consultation)

"This could be a viable option in order to address this type of research and bring the regulatory framework in line with internationally-agreed texts."

Consultation item no. 16: Do you agree with this appraisal? Please comment.

EFPIA and EVM joint response

With regard to the issue of emergency clinical trials, we confirm the views and suggestions submitted in EFPIA's response to the Consultation paper 2009/10 (consultation item no 15).

The proposal outlined in the concept paper published by the European Commission provides both an appropriate analysis and a viable solution in line with existing international agreements. Therefore we generally support the Commission's approach.

Key to the issue will be achieving a common understanding/definition of who can sign informed consent on the behalf of a patient who would benefit from entering an emergency clinical trial. For example a legal representative is in most countries not defined for healthy persons.

The rules applicable to emergency clinical trials will need to be fully harmonised and implemented in a consistent manner across the EU.

ENSURING COMPLIANCE WITH GOOD CLINICAL PRACTICES IN CLINICAL TRIALS PERFORMED IN THIRD COUNTRIES

"In view of the jurisdictional limits particular consideration should be paid to clinical trials in third countries where the data is submitted in the EU in the framework of the authorisation process of clinical trials and medicinal products……"

Consultation item no.17: Do you agree with this appraisal? Please comment.

EFPIA and EVM joint response

The Commission proposes three approaches for 'ensuring compliance with Good Clinical Practices in clinical trials performed in third countries 'as follows:

1) "*codifying in the revised legislative framework, the provision in point 2.7.2.4* of CT-1 "

2) "*further supporting capacity building in third countries where the regulatory framework for clinical trials, including its enforcement is weak"*

3) increasing "*transparency of clinical trials performed in third countries " by providing that "the results of these clinical trials are only accepted in the context of a marketing authorisation process in the EU if the trial had been registered in the EU clinical trials database EudraCT and thus be published via the public EU-database EudraPharm."*

EFPIA agrees with the first two proposed approaches. In particular,

- EFPIA supports further international cooperation in the regulation of clinical trials, encourages further dialogue with all stakeholders on GCP compliance and support the Commission's proposal with regard to capacity building in low and middle income countries to enhance local research infrastructure while respecting cultural differences.
- There is no objection to including point 2.7.2.4 of the detailed guidance CT-1 in the annexes to the basic legal act provided codification of these obligations (which must already be complied with) does not result in increased bureaucracy.

However we have some reservations concerning the third proposal and we recommend that rather than requesting registration in the EudraCT database it should be acceptable and sufficient to register clinical trials conducted exclusively outside the EEA in another public register, for example clinicaltrials.gov. Registering clinical trials conducted exclusively outside the EEA in

EudraCT provides no obvious benefit to EU patients. Therefore we suggest that focussing efforts on achieving consistency and integration between registers would result in improved/clearer communication on clinical trials thereby better serving the interests of the patient and health care professionals. Furthermore this would optimise the use of resources for both the persons who populate the databases and the bodies which host the databases.

Conversely we must acknowledge that the link between the act of registering a trial in EudraCT - EudraPharm and the ability to better assess data quality and GCP compliance is not clear and we do not believe that registering a trial on EudraCT will increase transparency of clinical trials performed in third countries. Firstly these studies will usually be registered in a public register as required under proposal 1. Secondly the results of studies included in the dossiers submitted to support applications for marketing authorisations are already made public in the EPAR. The EPAR puts into context the data obtained in the studies, in particular the relevance of any data from third countries to the EU population.