AESGP
Association Européenne des Spécialités Pharmaceutiques Grand Public
Association of the European Self-Medication Industry
Europäischer Verband der Arzneimittel-Hersteller

AESGP RESPONSE TO THE EUROPEAN COMMISSION CONCEPT PAPER ON THE REVISION OF THE 'CLINICAL TRIALS DIRECTIVE'

AESGP welcomes the opportunity to comment on the Concept paper on the revision of the Clinical Trials Directive.

We welcome the proposed revision of the Clinical Trials (CT) Directive. Protection of clinical trials' subjects and assurance of the robustness of the data are paramount in the carrying out of Clinical Trials and they are the two pillars of the Clinical Trials Directive. We appreciate the risk based approach combined with proportionate requirements proposed as an underlying theme to the revision of the Directive as we believe this will contribute to reduce unnecessary duplications and delays, administrative requirements and bureaucracy, and hence promote the conduct of clinical trials in Europe in both academic and non-academic settings.

1. Consultation item no. 1 - Single submission with separate assessment

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

Yes, we agree with this appraisal. We believe that a single electronic submission of Clinical Trial Applications for initial authorisation and any subsequent amendments through an EU portal, administered by the European Medicines Agency, would greatly reduce the administrative work of sponsors.

The advantage of such an approach would be to promote harmonisation and eliminate purely national requirements. The latter should be made clear in the text of the Directive and a similar language to the one used in article 107a(6) of the pharmacovigilance Directive could be used.
Although the responsibility of reviewing the documents and subsequently approving the trial would remain with the national authorities of the countries in which the study will be conducted, one pre-defined set of documents would significantly reduce the current preparation time and overall cost, it would increase reliability of project plans and free resources that could be mobilised for more important tasks in line with better regulation principles.

It should also be confirmed that this single submission via the EU portal will be a 'one stop shop' i.e. include submission to competent authorities and ethics committees. Countries with more than one ethics committee should find a solution that accommodates this single portal-single submission approach.

7, avenue de Tervuren • B-1040 Brussels • Belgium • Tel.: + 32 (0)2 735 51 30 • Fax: + 32 (0)2 735 52 22
E-mail: info@aesgp.be • http://www.aesgp.be

2. Consultation item no. 2 – Independent assessment by each Member State

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

Yes, we agree that separate assessments by the National Competent Authorities (NCAs) following a central single submission to an EU portal would not prevent sponsors from receiving divergent requests from those NCAs. However, defined submission requirements for the submission to a single EU portal would reduce the variety of requests coming from the NCAs and could therefore still significantly reduce the administrational work related to handling the responses to the various requests during the submission procedure.

3. Consultation item no. 3 – single submission with subsequent central assessment

This option would be a single submission (see above), after which the submitted information would be centrally assessed by a scientific committee made up of representatives of all the Member States. This option would be similar to the 'centralised marketing authorisation' for medicinal products.

Preliminary appraisal: 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. 1200) 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.

Yes, we agree with the appraisal as presented above although a central assessment could in theory be favourable for large multi-sites clinical trials and would be in line with the harmonised legal framework and single European review of the centralised procedure. This may however be premature and we also acknowledge the difficulty in centralising ethics committees' opinions.

4. Consultation item no. 4 – Single submission with a subsequent "coordinated assessment procedure" (CAP) – completeness of catalogue

This option would be a single submission (see above), which would be followed by a 'coordinated assessment procedure' (CAP). The CAP would be modelled, in some respects, on the decentralised procedure for marketing authorisations, while having a stronger element of joint assessment by the Member States concerned.

The CAP would:

- allow all Member States concerned to input to the assessment of the application for a clinical trial regarding the aspects set out below;

- provide for a ‘Reporting Member State’ whose role would be to lead the assessment of the application for a clinical trial;
- involve only the Member States concerned with a limited role for the Commission or the Agency – the latter acting as secretariat;
- only address certain aspects of the assessment of an application for a clinical trial
- lead to a ‘single decision’ per Member State which would include the aspects assessed in the CAP, as well as the ethical/local aspects of a clinical trial assessment.

The CAP would apply to the initial authorisation of a clinical trial, as well as subsequent 'substantial amendments'. Under the CAP, it would be up to each Member State to divide the tasks between the competent national authority and the Ethics Committee.

Preliminary appraisal: The CAP could offer a sufficiently flexible approach. It allows for a joint assessment without a cumbersome committee structure. It would allow national practice to be taken into account. It would respect that, as a basic rule, ethical issues clearly fall within the ambit of Member States.

Yes, we would consider the catalogue adequate and complete. However the last bullet point under a) “completeness and adequateness of the investigator’s brochure” should be broadened to “completeness and adequateness of background information” rather than pointing to the ‘investigator’s brochure’ which may not be ready at this stage or which may consist of background information on the safety of the medicine in some instances.

5. Consultation item no. 5 – Scope of the CAP

Scope: Only the risk-benefit assessment, as well as aspects related to quality of the medicines and their labeling would be suitable for the CAP. In particular, ethical aspects related to informed consent, recruitment and reward as well local aspects related to suitability of sites, the investigator, and national rules are not suitable for the CAP as they relate to ethical issues or to local expertise.

Yes, we agree to include only the aspects listed under a) in the scope of the CAP whereas b) and c) should be reviewed on a national level.

Generally, a CAP could be beneficial provided it is designed in such a way as to really streamline the procedure and reduce divergent opinions between Member States concerned. An essential pre-condition is that it does not add administrative burden nor delays.

In order for the procedure to be as efficient as possible, the regulatory and ethical reviews should operate in parallel. In the Concept Paper, it is mentioned that the CAP should lead to a ‘single decision’ per Member State which would include the aspects assessed in the CAP as well as the ethical/local aspects of a clinical trial assessment. The process to come to a ‘single decision’ will have to be clarified, at least at national level. Currently the ethical review in countries that have several local national Ethics Committees is a complex process which is very different from one country to the other. A better coordination at national level, such as that recently initiated in the UK and Belgium, would make the process smoother and improve the respect of timelines.

A number of issues remain unclear with regard to the functioning of the CAP in practice:

- The fact that the reporting Member State would 'lead' the assessment and the mention of "joint assessment" seems a bit contradictory. We think roles and responsibilities between Member States involved into the Clinical trials should be clear (i.e. who assesses what) with the "Reporting Member State" coordinating the various parts or steps of the assessment. In order to make the leading role of the Reporting Member State clear, we would propose "Leading (or coordinating) Member State". Furthermore, the decision on the choice of the "Reporting Member State" should be made based on an agreement between the sponsor and the given Member State (as it is the case in the DCP for example).

- The review process should be straightforward, simple and efficient to come to a fast harmonised decision with regard to the aspects listed in a) followed by a 'single national decision' at Member State level. It should be made clear that when the Member States have agreed on the aspects listed in a), there would not be the possibility to go back to their decision.

- To date there are different timelines for competent authorities and ethics committees for the review and approval of the submitted documents. This has shown to cause significant problems during the start up process of a clinical trial in the event that queries will be raised by the relevant body with the longer review times. We would therefore recommend harmonising these review times to prevent numerous submission cycles. The overall approval timeline should be of maximum 60 days for both competent authorities and ethics committees in all EU Member States. In the event of queries, responses can be provided within 90 days, but no clock-stop should be foreseen. The current practices and timeframes applied with regard to clock-stop in the various Member States indeed cause difficulties in planning clinical trials.
  There should be written approvals from competent authorities and ethics committees but no tacit approvals for interventional Clinical Trials anymore as those are not functioning in practice.

- There is currently no timeline in the Directive for Member States to raise "no grounds for non-acceptance" of substantial amendments and this is an important source of variability which impair the possibility to have clear timelines. Harmonised timelines for the review by competent authorities and ethics committees of substantial amendments should also be defined.

- This approach would require central/leading ethics committees in every Member State to allow a joint assessment procedure per Member State. If b) and c) remain on a national level, adequate timelines need to be implemented at national level for the suitability assessment of sites and investigators by potentially existing local ethics committees.

- Once the risk-benefit assessment is concluded positively and that the ethic review is performed and approvals are obtained e.g. in one Member State, the clinical trial should be able to start in that given Member State independently from the starting point in the other Member States so as not to generate unnecessary delays.

- What happens in case additional countries are added to the clinical trial ("repeat-use type procedure")? We believe that the country would get the submission as well as the CAP opinion which would hopefully help streamline the procedure in the added country.

6. Consultation item no. 6 – Disagreement with the assessment report

We would see the "simple majority" decision as the best option although it can be easily imagined that a country would not want to see its decision overridden by a collective vote and hence an opt-out should be possible for that country. The serious and justified concerns leading to an 'opting out' should have been tabled for discussion before the vote takes place with the aim of finding a consensus.
Although we fear that the last proposed option may generate delays, if requested by the sponsor, the opinion of the Clinical Trial Facilitation Group may be sought with the view to helping achieve consensus.

7. Consultation item no. 7 – Mandatory vs. optional use of the CAP

We would prefer the approach of CAP remaining optional as this would offer the most flexibility for the sponsor. The legislation should encompass a review clause of the optionality of the CAP after a couple of years. Based on the review (outcome and efficiency), the CAP could be changed and become mandatory for all multi-sites trials.

8. Consultation item no. 8 – Low-risk trials and shorter timelines

The general concept of shorter timelines for lower risk trials is in principle supported however the sponsor should actually decide based on a set of unambiguous criteria whether its clinical trial falls into the high risk or low risk tier. A system similar to that currently in operation in the UK with a table or Q&A defining the criteria could be an interesting option.

In any case, any delays due to a possible pre-assessment should be avoided. Hence, any pre-assessment should need to be performed by the EMA secretariat or the Reporting Member State during the very first step of the single submission procedure to the EU portal to allow subsequent adaptation of the timelines and should not exceed one week.

We believe that due to existing differences in clinical standard care across the MS within the EU, there could be huge differences in the (legal) interpretation of "standard treatment" and "normal clinical practice" in the different countries. In addition, the definition of "insignificant risk" posed by a Type A product might become a matter of national or even individual interpretation rather than a robust classification. We therefore fear that a pre-assessment would become a controversial and quite time consuming step potentially depleting the anticipated reduction of review time.

However if a pre-assessment is deemed absolutely needed then the timeline should be short (one week) and tacit approval ('silent assent') should apply once the deadline is passed.

9. Consultation item no. 9 – Scope of the Clinical Trials Directive

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

Observational studies do not require the same intensity of administrative work for both, applicant and reviewer, since due to the non-interventional nature of the trials, the safety-related aspects may be reduced or even inexistent. The inclusion of non-interventional trials into the scope of the Clinical Trials Directive would only be deemed beneficial if the requirements are truly proportionate to the low risk of the trial (no approval system, only notification), the timelines are significantly reduced and the administrative burden is reduced.

Non-interventional clinical trials should be subject to reduced timelines (maximum 15 days) and tacit approval should apply. The requirements would basically aim to guarantee that data generated are robust. Observational studies currently do not require national competent authorities' approvals in all Member States but only notifications. Such notification process should need to be reflected in the Clinical Trials Directive for non-interventional clinical trials. The German system is particularly pragmatic in that regard and we would advise that it is taken as model.

In accordance with the new provisions concerning non-interventional post-authorisation safety studies (PASS) in the new Pharmacovigilance legislation (notably chapter 4, article 107m), the study protocol will have to be evaluated and authorised by the Pharmacovigilance Risk Assessment Committee (PRAC). This new legal requirement needs to be considered when developing a comprehensive system in order to avoid any potential duplication.

It is of paramount importance that the inclusion of non-interventional trials in the new Clinical Trials Directive be subject to requirements, process and timelines proportionate to the extremely low risk of these trials. If this cannot be guaranteed, non-interventional clinical trials should better remain outside of the scope of the Directive.

10. Consultation item no. 10 – Nature of sponsor (academic vs. commercial)

Preliminary appraisal: 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. These proportionate requirements would apply independently of the nature of the sponsor ('commercial' or 'academic/non-commercial').

Yes, we do agree with this appraisal. It is in the interest of any sponsor (operating in commercial or academic structure) to achieve the highest quality and best protection standards for the subjects included in a clinical trial and produce robust and reliable data.

11. Consultation item no. 11 – A more precise and risk-adapted rules for the content of the application dossier and safety reporting

Preliminary appraisal: 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.

This is agreed as the proposed approach would definitely simplify, clarify and streamline the rules for conducting clinical trials within the EU and avoid national divergences.

However, we fear that the update of the Annexes may be difficult and that "normal clinical practice" will remain a matter of local interpretation and comparison to the risk to trial subject safety will therefore remain limited.

12. Consultation item no. 12 – Other key aspects missing

To our view this is complete.

13. Consultation item no. 13 – Clarification of the definition of 'investigational medicinal products' and establishing rules for 'auxiliary medicinal products'

- The definition of IMP could be changed and clarified by narrowing it as follows: 'A medicinal product which falls within the definition of Article 3(3) of Directive 2001/83/EC, and which is being tested or used as reference in a clinical trial.' This would ensure that only the medicines that are the object of the study are covered by the requirements for IMP;
- The notion of 'auxiliary medicinal product', covering all other medicinal products used in the context of the clinical trial, could be introduced: 'A medicinal product as referred to in Article 3(3) of Directive 2001/83/EC which is not an investigational medicinal product';
- 'Auxiliary medicinal products' could be subjected to a proportionate regulatory regime, which would be separate from IMPs; and
- The rules for dossier requirements, reporting, and labelling for both IMPs and auxiliary medicinal products could be set out in the Annex to the basic legal act (see point 2.2).

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

We would highly appreciate a separation of auxiliary medicinal products from the definition of the actual IMPs and having rules for dossier requirements being annexed to the Clinical Trials Directive so as to promote harmonisation and prevent national requirements. Therefore we agree with the proposed appraisal. Clearly, the definitions for IMP and non-IMP need to be highly specific and sufficiently robust and the requirements should follow a risk-based approach.

Divergent requirements exist in different Member States for the labelling of IMPs, some requiring the application of the GCP Regulation and others Annex 13 of the GMP guide; hence harmonisation would be particularly beneficial in this area.

14. Consultation item no. 14 – Insurance and indemnisation

In order to address this situation, several policy options could be considered, such as:

- Removing insurance/indemnisation requirements for low-risk trials: This policy option would remove the insurance requirement for clinical trials which typically pose a low risk for trial subjects or;

- Optional indemnisation by Member State: This policy option would put Member States under an obligation to provide for an indemnisation for damages incurred during clinical trials performed in their territory, taking account the national legal system for liability. In view of the damages arising today, the burden on national budgets would be minimal.

Preliminary appraisal: Both policy options could be a viable solution.

We do not see the complete removal of insurance/indemnisation requirements for low-risk trials as a viable approach; rather the classification of a trial as a 'low-risk' trial could be useful to get lower insurance premiums.

15. Consultation item no. 15 – Single sponsor

The Clinical Trials Directive is based on the concept of a 'single sponsor' per trial. The single sponsor is 'responsible' for the trial vis-à-vis the national competent authority and the Ethics Committee.
It is a recurrent criticism that the concept of a 'single sponsor' renders multinational clinical trials more onerous.
Two options could be considered:
- Option 1: maintaining the concept of a single sponsor;
- Option 2: allowing for a 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 trial in a Member State.

Preliminary appraisal: 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 harmonized.

We prefer option 1 to maintain the concept of a single sponsor with the provisions given in the preliminary appraisal.

16. Consultation item no. 16 – Emergency clinical trials

No comments – this type of trials is outside our remit.

17. Consultation item no. 17 – Clinical Trials performed in third countries

Both provisions, as well as implementation work could be further supported and supplemented through the following:
- Codifying, in the revised legislative framework, the provision in point 2.7.2.4.of the detailed guidance CT-1; and

- Further supporting capacity building in third countries where the regulatory framework for clinical trials, including its enforcement is weak.

In addition, in order to increase transparency of clinical trials performed in third countries the legislation could provide 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.

We believe that any initiative which will increase compliance with GCP in third countries will be of great benefit for the safety of subjects and the quality of the data.

The submission of GCP compliance statements for trials conducted outside the EEA appears feasible, whereas references to public register entries may become more challenging, especially when a justification for no publication will become required. We think that such an approach will require a list of acceptable public databases and a harmonised understanding of what the minimum information are to be disclosed to the public.

18. Consultation item no. 18

No comments.

13 May 2011