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

AESGP RESPONSE TO THE COMMISSION'S CONSULTATION ON THE ASSESSMENT OF THE FUNCTIONING OF THE "CLINICAL TRIALS DIRECTIVE" 2001/20/EC

AESGP appreciates the opportunity of being consulted on the functioning of the Directive on Clinical trials.

Consultation item n° 1 - "achievements"

Can you give examples for an improved protection? Are you aware of studies/data showing the benefits of the Clinical Trials Directive?

The Directive has laid down a pan-European harmonised approach aiming at ensuring patient safety via the standardisation of informed consent, the monitoring of adverse reactions, etc. which is obviously positive. However, from a practical point of view and comparing the overall benefit versus the practical issues encountered by the industry, the assessment unfortunately comes negative from an industry point of view.

Our search mostly resulted in studies or articles illustrating issues caused by the Directive, in particular in the performance of trials by academia[1][2][3][4]. Only one article contradicted this opinion by showing that academic clinical trials had not been negatively affected in Denmark[5].

KEY ISSUE N°1 TO BE ADDRESSED: MULTIPLE AND DIVERGENT ASSESSMENTS OF CLINICAL TRIALS

Consultation item n°2

Is this an accurate description of the situation? What is your appraisal of the situation?

We agree with this description.

According to the views expressed by our members, and although the conduct of multinational clinical trials was eased by the harmonisation brought by the Directive, the administrative requirements and costs have clearly escalated after the transposition of the Clinical Trials Directive into national legislations. The scale of complexity and heterogeneity in the assessment process of a Clinical Trial application is illustrated in the table prepared by the Clinical Trial Facilitation Group[6].

[1] http://jnci.oxfordjournals.org/cgi/reprint/jnci;98/3/159.pdf
[2] http://www.plosmedicine.org/article/info:doi%2F10.1371%2Fjournal.pmed.1000131
[3] http://www.ecrmforum.org/press/BMJ_03.pdf
[4] http://www.eahp.eu/content/download/29283/186848/file/CoverStory18-19.pdf
[5] http://www.outsourcing-pharma.com/Clinical-Development/EU-s-Clinical-Trial-Directive-put-no-brake-on-trials and http://www.dkma.dk/1024/visUKLSArtikel.asp?artikelID=13921
[6] http://www.hma.eu/uploads/media/Assessment_in_MS_public_dec_08__2_B.pdf

Although the Clinical Trial Directive has introduced some degree of harmonisation in the issues Ethics Committees should look at and the timing for doing so, the functioning of Ethics Committees remains highly heterogeneous between Member States[7], which is the cause of additional complexity and unpredictability to sponsors. Some countries have one central Ethics Committee whilst others still have regional/local Ethics Committees. Their composition, the level of compensation (fees) requested, the respect of timelines[8] and their functioning is also quite different from one country to the other, which requires the sponsor to have an elaborated knowledge of the national system(s) where trials are to be performed.

The variations and divergences in the content of the clinical trial application, post-authorisation studies requirements, changes in the protocol and local/regional monitoring of adverse events all have a negative repercussion on resources and timing of clinical trials without or with disputable added-value for the patient. The level of bureaucracy requires increased staff, resources and time.

For example, if a Clinical Trial protocol is approved by a majority of Member States concerned but one Member State disagrees, then if it is a minor change, the clinical trial goes on with slightly different protocols between Member States or if it is a substantial amendment, the national competent authorities and Ethic committees need to be notified. This could lead to a change in the protocol and restart of the trial.

One of the main issues has to do with the interpretation of what is a 'substantial amendment'. Although four criteria are laid out in the *Detailed guidance for the request for authorisation of a clinical trial on a medicinal product for human use to the competent authorities, notification of substantial amendments and declaration of the end of the trial,* their interpretation is quite variable from one Member State to the other and even within one Member State.
For example, in some Member States, the 'extension of duration of a trial' is considered a substantial amendment!
Another example has to do with changes of medication labels and updates of the investigator's brochure (without a change in the risk-benefit assessment) which in a specific case were considered substantial amendments in one country whereas the other Member States involved thought otherwise.

To address this problem, we propose that a short definition of 'substantial amendments' emphasising the notion of patient safety be introduced in the revised legislation. In addition, taking the system used for 'potential serious risk to public health' examples, we suggest that Volume 10 is complemented with a living annex providing examples of what may be and what is not a 'substantial amendment'.

[7] http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2563384/
[8] http://www.google.be/url?q=http://www.eahp.eu/content/download/29283/186848/file/CoverStory18-19.pdf&ei=Hf1GS7voB9iM4gbGpoyBAw&sa=X&oi=spellmeleon_result&resnum=1&ct=result&ved=0CAcQhgIwAA&usg=AFQjCNG2HB1ov6EdTDSZtnpOC9y72rK8Fw

To add to the complexity, the notion of possible effect on 'patient safety' is also sometimes interpreted differently by Ethics Committees.

Besides the issue of substantial amendments, additional issues needing better harmonisation include:

- Timeframe for the approval of clinical trial applications and of substantial amendments:

Despite the theoretical limit of 60 days, difficulties in planning clinical trials arise because of different timeframes applied with regard for example to clock stop in different Member States.
In addition, no timeline is indicated in the Directive for Member States to raise "no grounds for non-acceptance" of the substantial amendments and this is an important source of variability which impair the possibility to have clear timelines.

- Implicit or explicit approval

An explicit approval would offer the advantage of an official document that could be maintained in the context of the Trial Master File and shown during an inspection. An explicit approval would provide more certainty and reliability to the applicant.

Consultation item nº 3

Is this an accurate description? Can you quantify the impacts? Are there other examples of consequences?

We agree with this description. The main consequences are in terms of timing and resources.

Consultation item nº 4

Can you give indications/quantifications/examples for the impact of each option? Which option is preferable? What practical/legal aspects would need to be considered in further detail?

1) In terms of voluntary cooperation: we wonder whether there could be scope to use the EudraCT database to upload information concerning pre-authorisation.

By analogy with the Common Technical Document, we would also suggest a common format for the Clinical Trial Application (CTA) is adopted and is either annexed or clearly referred to in the Directive.

2-A) The principle of a common agreement would already be helpful however we have some reservations as to how this would work in practice given the already relatively recent nature of the European Clinical Trial framework. To make a comparison, issues are still encountered in the MRP-DCP for evaluation of marketing authorisation applications although the procedure is much older, structures well in place and Member States accustomed to such procedures.
Hence, this could be an option if, as a prerequisite, there is a clear buy-in from Member States and commitment to abide by the timelines and recommendations.

In addition, to help reach consensus, the Clinical Trial Facilitation Group could be formalised and have a role similar to that played by the Coordination group in the MRP/DCP.

We would also suggest that a similar procedure should be considered for Ethics Committees. This would be particularly important in case of multinational trials.
2-B) The possibility of going central for multinational clinical trials would indeed be helpful as it would provide for one opinion at the end and may also contribute to a better understanding of national practices between Member States and a more level-playing field in the long run. However, the centralised system as we currently know it would need to be adapted as in no case all 27 Member States would be involved in the multinational clinical trials. We believe the use of a central procedure should be voluntary and its scope somewhat restricted, as a start, to disease areas highlighted in the mandatory scope of Regulation 726/2004.

Consultation item nº 5

Can you give indications/quantifications/examples for the impact of each option? Which option is preferable? What practical/legal aspects would need to be considered in further detail?

Ethics Committees add a level of complexity at national level. AESGP strongly support the proposal of one-stop shop for the submission of assessment dossiers. We also support strengthening the network of the Ethics Committees involved in multinational CTs and even to form a platform or an ad hoc group that could ideally come to a common opinion (cf. consultation item above).
For countries having regional/local Ethics Committees, it would be desirable that they become more specialised/dedicated to a therapeutic segment/disease so that in the option envisaged above, the Ethics Committee seating at the table of discussion would be automatically decided by the indication investigated.

Consultation item nº 6

Is this an accurate description of the situation? Can you give other examples?

We agree on the three points.

Substantial amendment: We refer to consultation point # 2. Some companies tend to submit all non-substantial amendments to the authorities for information in reaction to the tendency from a majority of authorities to consider many “non-substantial amendments” as “substantial ones”. The same wide range of reactions is applicable within some agencies as well where the response on whether a change is substantial or not depends on who is asked.

Consultation item nº 7

Is this an accurate description? Can you quantify the impacts? Are there other examples of consequences?

Yes, we agree with the description.
Phase IV trials are also sometimes subject to differing interpretation by Member States.

We agree that the divergence in SUSAR reporting requirements has created a complex system. In order to lower the administrative burden within the current system without undermining patient protection, we would recommend that local SUSARs need to be notified only to the respective NCAs and that all SUSARs be made available to all Agencies via EudraVigilance and the provision of the annual Safety Report.
The prices of insurances drive prices up and it becomes difficult to find insurances that accept multinational trials.

Consultation item nº 8

Can you give indications/quantifications/examples for the impact of each option? Which option is preferable? What practical/legal aspects would need to be considered in further detail? In particular, are the divergent applications really a consequence of transposing national laws, or rather their concrete application on a case-by-case basis?

An amendment of the Directive would allow keeping some flexibility at national level, which may be of benefit for smaller companies running trials in only one country. However, this would mean that harmonisation is never 100% complete.
The advantage of a Regulation is that the text is immediately binding in 27 Member States and supersedes national requirements, with no delays caused by transposition time. The resulting harmonisation is real, instant and effective. Nevertheless, we see the risk that the most stringent requirements become the EU model in the end.
We would say that global companies may prefer a Regulation whilst smaller, purely national company may be fine with a modification of the Directive which may overall entail less change in the country in which they operate.
As representatives of a majority of small companies, we think that a revision of the existing Directive would be more realistic and targeted.

Consultation item nº 9

Can you give examples for an insufficient risk-differentiation? How should this be addressed?

This is of particular relevance to whether or not the IMP is already authorised in the EU or elsewhere. Specifically for the Investigational Medicinal Products Dossier (IMPD) there is an option of submitting a simplified IMPD based on the established safety profile of the active known to the concerned authority.

There are circumstances where cosmetic products may be the current standard of care or where a clinical trial application (CTA) is required to support cosmetic claims. According to the European Cosmetic Directive "keep in good condition" is a cosmetic claim, supporting this claim for some cosmetic products (e.g. skin care or oral care) can best be achieved by the measurement of disease markers to establish whether a good condition is being kept or not. Thus, a study using an investigational product, compliant in intended use and ingredients with the European Cosmetics Directive, can become a clinical trial, purely by the measurements that are being taken. In most circumstances, these investigational products are unlikely to contain actives for which an MAA had been obtained and a simplified IMPD is not currently an option. Thus, a product would have a safety profile that would enable commercial launch without any pre-approval, and yet a full Investigational Medicinal Products Dossier is required to be submitted to enable conduct of a clinical trial to support either verification of the current standard of care or to verify certain cosmetic claims! The principle of a simplified IMPD has already been established for medicines with a known safety profile. Building on this principle and with the aim of achieving Better Regulation and reducing the regulatory burden for ingredients whose safety profile has already been established, under other EU legislation, there should be a simplified route for this type of submission that is appropriate to the intended use and formulation.

This could be addressed by:

1. Clarification that a clinical trial conducted on cosmetic formulations, which require measurement of medicinal markers to support cosmetic claims, does not require a CTA.

2. In circumstances where a CTA is required, and the IMP complies with the European Cosmetic Directive there is a route for simplification of information to be supplied, e.g. submission of a declaration that the ingredients and the intended use are compliant with the European Cosmetic Directive and a copy of the intended labelling or submission of a Product Information File, or a simplified IMPD.

Labelling of IMPs: Here again, divergent requirements exist in different Member States; some requiring the application of the GCP Regulation and others Annex 13 of the GMP Guide. Harmonisation would be beneficial in this area.

Consultation item nº 10

Do you agree with this description? Can you give other examples?

We generally agree with this description.

Consultation item nº 11

Can a revision of guidelines address this problem in a satisfactory way? Which guidelines would need revision, and in what sense, in order to address the problem?

We refer to our comment made under consultation item #9. Table 1. "Reduced information requirements for IMPs known to the concerned competent authority" of the "Detailed guidance for the request for authorisation of a clinical trial on a medicinal product for human use to the competent authorities notification of substantial amendments and declaration of the end of the trial - October 2005" states the criteria for which reduced information can be submitted. Revising the guidance and in particular adding as new criterion "submission of a declaration of conformity to the European Cosmetics Directive or the Cosmetic Product Information File or of a simplified IMPD" would address this issue.

Consultation item nº 12

In what areas would an amendment of the Clinical Trials Directive be required in order to address the issue? If this was addressed, can the impacts be described and quantified?

We believe that most of the text would need to be considered for revision.

Consultation item nº 13

Would you agree to this option and if so what would be the impact?

We oppose a two-tier system. For patient safety, we think it is important to have legislation with the basic principles applying to all and that may include specific exemptions or provisions for academic sponsors and proportionate approach based on risk to trial subjects.

Consultation item nº 14

In terms of clinical trials regulation, what options could be considered in order to promote clinical research for paediatric medicines, while safeguarding the safety of the clinical trial participants?

It is our understanding that the issues have more to do with the Paediatric regulation and the divergences in opinion between the Ethics Committees and the Paediatric Committee on Paediatric Investigation Plans they issue. Therefore, we do not believe that the clinical trial legislation would need modification to promote paediatric trials. The legislation as such does not create specific hurdles for conducting clinical trials in children. In any case, the requirements for all clinical studies should follow the same core principles.
Incentives are needed but this should not be the place to address them.

Consultation item nº 15

Should this issue be addressed? Which ways have been found in order to reconcile patient's rights and the peculiarities of emergency clinical trials? Which approach is favourable in view of past experiences?

This is not really relevant or applicable to our sector so we will skip this consultation item. However we have found an article[9]- that may help address the second question.

Consultation item nº 16

Please comment? Do you have any additional info, including quantitative information and data?

It is the responsibility of sponsor and company to check that GCP are enforced and it should remain so. Sponsors usually have internal quality control and assurance functions to ensure robust data generation, data integrity and GCP compliance. Statements to certify GCP and GMP compliance are included in the regulatory submission.
EU led support programmes to facilitate capacity building in third countries for supervision of international principles could be an option.

Consultation item nº 17

What other options could be considered, taking into account the legal and practical limitations?

Sponsors and companies are responsible and we would oppose any additional legislation. A stronger international cooperation, capacity building could be explored as well.

Consultation item nº 18

What other aspects would you like to highlight in view of ensuring the better regulation principles? Do you have additional comments? Are SME aspects already fully taken into account?

It would be useful to have the notion of co-investigator being included in the legislation as well. The liability would remain with the investigator but the co-investigator could be delegated some tasks.

14 January 2010

[9] available at: http://www.univie.ac.at/ierm/php/Dokumente/BMJ_Artikel_Original.pdf