Statement of the Federal Institute for Drugs and Medical Devices and the Federal Institute for Vaccines and Biomedicines (Paul Ehrlich Institute)

on the

public consultation on the

"Revision of the Clinical Trial Directive 2001/20/EC" of the European Commission of 9th February 2011

May 2011

Preliminary remarks

The higher federal authorities responsible for the approval of clinical trials in Germany – the Federal Institute for Drugs and Medical Devices *(BfArM)* and the Paul Ehrlich Institute *(PEI)* – welcome the consultation and the ensuing discussion process and thank the Commission for the opportunity to submit comments.

Directive 2001/20/EC has achieved essential improvements in the safety and credibility of the data resulting from clinical trials. At the same time, we agree with the Commission that the procedure for authorising clinical trials can be simplified further, without having to compromise on the objectives of the directive in question.

This also includes an assessment of whether, instead of submitting the same application for approval to several competent authorities in different member states, it would not be prudent from an expert perspective, but also organisationally and technically feasible (for example regarding the databases which would then need to be maintained), to have such submissions made to a single, central point. In the process, the question also arises as to whether such central submissions would be appropriate for all clinical trials. Should the central submission procedure apply only when the clinical trial in question is to be conducted in more than two or three member states (to our knowledge that would account for approximately only one-quarter of the trials conducted) this would render the central submission procedure more effective.

In 2008 , the national authorities already started to address the point of central submission of clinical trial applications since the practical implementation of the approval procedure for such multinational trials has, in the past, given rise to difficulties which have to be avoided. This circumstance has led national competent authorities to develop the voluntary harmonisation procedure (VHP) which is a procedure to enable the simultaneous submission of applications in several member states. This procedure, which is in practice since 2009, has experienced a very positive reception from both sponsors and the competent authorities. One aspect of this procedure which is worthy of special mention is the high efficiency by its flexible design. The procedure sets up the co-ordination process between the competent authorities. It enables harmonised decisions within appropriate timelines, while taking into account national perspectives (indispensable, for example, where ethical considerations are concerned).

It would be desirable for the experience gained hitherto with the voluntary harmonisation procedure to be further developed and to be integrated in the Directive 2001/20/EC. The

already established voluntary procedure couldeven be expanded and established as opposed to a binding, central procedure.

To keep this commentary transparent, the Commission's proposals will not be reiterated here. Instead, direct reference will be made to the Commission's individual questions or proposals.

1. Co-operation in assessing and following up applications for clinical trials.

1.1 "Single submission with separate assessment"

Consultation item 1: Do you agree to the proposal of a 'single submission'?

In principle, the Federal Institute for Drugs and Medical Devices *(BfArM)* and the Paul Ehrlich Institute *(PEI)* welcome the concept of a central submission. However, certain regulatory and technical prerequisites, which are described in greater detail below, must be fulfilled before the exclusive and binding utilisation of such a central portal can be possible. As a basic principle, the Commission should come to a decision on common regulatory and technical prerequisites – by common agreement with the Member States – since the latter essentially bear the responsibility for the clinical trial and must therefore have the possibility to influence its design.

- In addition to the *per se* very high technical requirements that such a central portal must meet, this central repository should also be responsible for authentifying the applicant seeking to conduct a clinical trial. To date, the development of EudraCT, over what has been a period of more than seven years, shows that it was not always possible to process even a simple application submission technically without problems (cf. EudraCT update to Version 8).
- The initial validation of an application, to determine formal conformity, is handled differently by the various member states. Germany's experience has shown that a purely technical validation, to determine whether a specific document has been submitted or not, is frequently insufficient. If a faulty document is not recognised in this initial validation stage, and only comes to light at a later date, during the assessment of content, it will only be possible to assess the corrected, complete document during the phase reserved for the elimination of grounds for non-acceptance. In such a case, flaws regarding the contents should consequently lead to the immediate rejection of the application, since the submission of reasoned grounds for non-acceptance would no longer be possible. An application should only be considered valid, and therefore be accepted, if both the technical validation of formal conformity and the orienting validation of its contents have been conducted.
- In the event that reference is made to previously submitted documents, it should be possible for a subsequent other applicant to make reference to the already submitted documents – as has hitherto been the case – only with the permission of the initial applicant.
- Since, according to the 'concept paper' a central portal is also meant to be used for mono-national studies which – with more than 70 % – account for the majority of clinical trials in the approval process, it must be ensured that this portal can be accessed in each country's national language.
- When the portal meets the described prerequisites, and is fully functional, central submission via the portal should be obligatory and hardcopy submissions should no longer be admissible.
- Since the Directive allows for national perspectives, such as a statement on the gender-specific aspects of the clinical trial – as is the case in Germany – the portal should allow for country-specific documents to be submitted with the application. The absence of such documents must then consequently also be regarded as a validation flaw.

Consultation item 2: "Separate assessment"

According to the trial figures presented under point 4, only 25% of all clinical trials are conducted in more than one member state. Consequently, even after the technical conditions have been created for a European submission portal, a national submission of applications to the competent national authority should continue to be a possibility so as to reduce the bureaucratic burden for sponsors and authorities. The 'Coordinated Assessment Procedure' (CAP) presented in the Commission's document should, if at all, only be an option for multinational procedures involving at least two member states, so as to render the additional administrative effort and costs justifiable.

1.2 Single submission with subsequent central assessment

Consultation item 3: "Central assessment and central approval of multi-national clinical trials"

The Federal Institute for Drugs and Medical Devices *(BfArM)* and the Paul Ehrlich Institute *(PEI)* support the Commission's opinion that such a central assessment and – possibly – approval procedure will increase the procedural complexity, duration and costs and is therefore not suited to the approval procedure for national clinical trials, since approximately 75% of all clinical trials are conducted exclusively at national level. The comparison with the 'centralised marketing authorisation' should not be drawn since, in the central procedure, one rapporteur and one co-rapporteur conduct the assessment and the remaining European countries often do not carry out an independent assessment of their own. In the case of a clinical trial with medicinal products which do not have a marketing authorisation for the indication under investigation, the risk of damage to the exposed population is not precisely known and potentially always higher than in the case of an application for a marketing authorisation, since not all of the medicinal products which are tested necessarily reach the stage where an application is made for a marketing authorisation; in some cases, the development programme is prematurely terminated due to absence of a positive risk-benefit assessment or because the planned indication has been abandoned. As a result, we deem it necessary for the member states to retain their own competence in deciding on the conduct of a clinical trial on their sovereign territory on their own responsibility.

1.3 'Coordinated Assessment Procedure', CAP

With regard to the CAP, it should be noted that terms taken from the marketing authorisation procedure should be avoided when speaking about clinical trial procedures so as to avoid confusion. For instance, the abbreviation 'RMS' in the decentralised marketing authorisation procedure refers to the 'reference member state', whereas the abbreviation 'RMS' in the CAP stands for 'reporting member state'. We therefore advise that confusion be averted by finding clear terms to describe new procedures.

With regard to the vertices of the CAP in detail:

The Voluntary Harmonisation Procedure (VHP) developed by the Clinical Trial Facilitation Group (CTFG) of the Heads of Medicines Agencies, and continually optimised by suggestions for improvement from sponsors and national competent authorities, enjoys wide acceptance among the competent authorities and, precisely since the beginning of 2011, a clearly increasing recognition and acceptance among the sponsors. We therefore propose that this procedure, which has been field-tested and adapted to the requirements of the sponsors and the national authorities, be incorporated into the Directive, as a multinational procedure, in the course of the revision of Directive 2001/20/EC. We have not been able to find any advantage in the CAP at the moment which exceeds that of the VHP. Precisely the flexibility of the VHP, which is created by consensus building among the Member States on concrete questions, makes this procedure attractive to sponsors in its current form.

Independently of its name, the establishment of a multinational procedure by law has our support, in principle, as long as it involves two or more member states. Every multi-state procedure should culminate in the approval and the payment of fees for the approval of the clinical trial pursuant to the provisions laid down by the Member State.

The Federal Institute for Drugs and Medical Devices *(BfArM)* and the Paul Ehrlich Institute *(PEI)* are of the opinion that each Concerned Member State should have the right – as already actively practiced in the VHP – to make a contribution to the assessment of the clinical trial, in the form of comments or objections, so as to ensure that the trial for which an application is submitted is consistent with national circumstances and perspectives. Should this not be the case, there is a danger that the decision regarding the risk to which trial subjects in a member state are exposed is taken by another member state, even though the member state taking the decision bears no responsibility in the territory where trial is is conducted. Even though the concept of harmonisation is an important one, and one which is actively supported by both authorities, we should recognise that medical standards vary among the different member states and this should be taken into account in deciding on an approval.

The role of the Reporting Member State (RMS) should be to co-ordinate the assessment (to 'co-ordinate' instead of 'to lead'). Should the Co-ordinating Member State and a Concerned Member State (CMS) arrive at different assessments, the grounds for non-acceptance (GNAs) submitted by the Concerned Member State must be communicated to the sponsor or applicant for approval so that these objections can be satisfactorily clarified or remedied. The procedure should as far as possible, for the reasons mentioned above, prevent a RMS from being in a position to pass over or overrule a CMS or CMSs.

The question also arises as to who selects the RMS and according to what criteria the selection is made. The co-ordinating RMS should be chosen on a rational basis. A suitable committee such as the CTFG should be responsible for selecting the RMS and/or allocating the trials. This could be done on the basis of a voluntary indication of interest or can be based on a formula, for example the number of multinational clinical trials in the EU/EEA. In addition, appropriate expertise should be available. We do not consider it useful for the sponsor to be granted a right to submit a proposal or to decide.

With regard to the Concerned Member States, it should be clear that those Member States which will only become involved at a later stage – namely after the original multinational procedure has run its course – must have full access to the application documents and to the assessment, as well as a right to decide, at national level, on the approval of the clinical trial.

For the management of such a co-ordinated assessment procedure, we propose a co-ordination body hosted at the CTFG which, as with the currently offered VHP, will ensure that procedures are unbureaucratic and inexpensive. Such a body could also be responsible for the repository which holds application documents and Member States' contributions at the latter's disposal. The 'limited role' of the Commission or EMA bodies in the CAP procedure, suggested in the Commission's proposal, should be avoided owing to an absence of competent jurisdiction in the area of clinical trials and for reasons of procedural efficiency.

The proposed "single decision per Member State" regulation seems highly promising. Nevertheless, it should be made clear that what is meant is an 'agreement' between the national competent authority and the Ethics Committee on one approval – something which was not envisaged previously in this form by the Directive. Whereas the procedures hitherto have been completely independent of one another, and could be addressed either consecutively or parallel, one decision-making body now has to wait on the other. Ethics Committees according to the ICH-GCP are, *per se*, independent – therefore also in their decisions – and are not bound by instructions from the authority. Overlapping assessments are desired and

divergent votes are rare but possible, based on the different aspects of the assessment of a clinical trial.

A strict division of the tasks, which do not require an assessment by the Ethics Committee, as listed under Point 1.3.1 of the concept paper, is not deemed to be appropriate. The Ethics Committee should also have the right – as is the case in Germany – to assess the study protocol and the investigator's brochure. Under these circumstances, a single decision per Member State within 60 days is almost impossible. Furthermore, we can already observe today, that the national authorisation periods are longest subsequent to a VHP in those Member States where the authorities and the Ethics Committees have to decide jointly. The adoption of this approach is therefore not likely to be the ideal method for promoting fast and flexible decisions.

Moreover, mixing a discussion about the roles and/or responsibilities of national competent authorities and Ethics Committees with a discussion on a multinational approval procedure should be avoided. Should the Commission wish to explicitly regulate the tasks incumbent on the authorities and the Ethics Committees, this should not be done in a procedural context but in another framework, whereby the independence of the national competent authorities and Ethics Committees should continue to be upheld, even if tasks overlap.

The possibility of the simultaneous submission of applications to authorities and Ethics Committees is already being implemented in Germany and, as such, we explicitly welcome it.

1.3.1 Scope of the CAP

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

The aspects already mentioned, listed in Section 1.3.1, should be handled in accordance with the ICH's Note for Guidance on Good Clinical Practice (ICH E6) and the Helsinki Declaration. The catalogue under a) to c) is incomplete; we propose the following additional points:

re: a)

- The risk benefit analysis should include an assessment of the risk management of the clinical trial.
- Depending on the trial design, the statistical background (for example, the appropriate number of participants) should be assessed as well.
- Regarding the trial design, the entire protocol, for example the reporting of safety alerts etc., should be assessed.
- The relevance of the trial should include its scientific justification.
- Alongside the assessment of the efficacy of the investigational medicinal product, the standard therapy of the indications under investigation should also be included.
- With respect to the labelling of the investigational medicinal product, in the course of harmonisation, a generic master label in English should be submitted. In the light of the blatant shortcomings of the past, it is necessary for a label translated into the national language of the Concerned Member States to be submitted as well.
- In addition to the investigator's brochure, the entire documentation on the investigational medicinal product should be assessed. Depending on the concept of the trial, this documentation could also include other appropriate documents such as the summary of product characteristics (SmPC).

re: b)

Here, the ethical aspects of the trial and of the medical conditions should also be taken into account. The process for receiving informed consent should also be subject to this evaluation.

Consultation item 5: "Only aspects under a) in scope of CAP"

In principle, we support the approach of only assessing the points listed under a) in a CAP procedure. For the reasons already mentioned above, we see no additional benefit in the 'single decision per Member State' procedure for the sponsors, authorities and, above all, for the persons affected by the clinical trial. Instead, in keeping with the spirit of the GCP, we favour the principle espoused hitherto of the independence of the Ethics Committees and the authorities.

1.3.2 Disagreement with the assessment report

Consultation item 6: "Disagreement with assessment report"

We take a critical view of the three options proposed here. In particular, we miss the possibility to make improvements to clinical trials even after objections by the imposition of duties or the partial refusal of the authorisation by the authority in order to increase patient safety and/or the credibility of the trial results. As has been shown in the past, simple 'yes' or 'no' decisions do not always do justice to this set of issues.

With respect to the Commission's proposals in detail:

- "opt out ... serious risk to"
  The 'opting out' of a member state on basis that the clinical trial constitutes a serious risk and concerns the risk-benefit-assessment is, in general, not a purely national problem. However, an 'opting out' might – though rarely – be based on national circumstances, for example: national legislation or normal medical practice, for instance regarding: radioactivity, trials involving minors or pregnant women, standard therapies and the like.

- "vote by simple majority" and "EU level decision"
  This is difficult to justify from an ethical perspective. A trial should not be conducted in a member state which entertains serious doubts about the trial. The responsibility of a concerned member state, on the territory of which the trial is to be conducted, should by no means be imposed by majority vote or as an “EU-level decision”.

Instead, we propose that in the (very) rare cases in which the aspired unambiguous decision is not possible, the option of withdrawing from the CAP procedure at the end of the procedure should be envisaged. This should be independent of the magnitude of the risk to public health or to the safety of patients. At the same time, it should be possible for the sponsor to submit the application at national level and thus take into account the necessary national, local or ethical modifications. This procedure has so far proven its worth in the context of the VHP. The experience gleaned from approximately 80 VHP procedures shows that non-concurring opinions or additional national requirements and conditions constitute a rare exception.

1.3.3 "Mandatory/optional use"

Consultation item 7: "Mandatory/optional use"

Of the three options presented, the option of a binding CAP inclusion of all clinical trials (mono-national and multinational) cannot be advocated for the reasons already discussed, since the additional costs – like those incurred in a multinational trial – would not be justifiable in the case of a purely national trial. In the latter instance, the third option of an optional CAP, based on the sponsor's decision, should be seen as the only option. However, for reasons of efficiency, a CAP should be possible, only if at least two member states are involved.

1.3.4 "Tacit approval and timelines"

We support the Commission's proposal that, in the CAP, no 'tacit approval', in other words, the implicit approval after the fixed procedural period has elapsed if no objections have been raised by the assessing authorities, should be allowed, so that an (official) notification is obligatory. In this context, it should be considered that each timeline begins to run only after the full validation of formal conformity of the application has been confirmed. This technical and scientific validation, and with it the starting date, should be confirmed by the RMS. This is absolutely necessary (especially) in the case of reduced timelines.

With respect to the times for the CAP and the approval of clinical trials, we generally recommend a 'clock stop' for the sponsor of the clinical trial to comment on the objections raised. This should be limited in time, as is already the case in Germany. The desire for such a 'clock stop' has been frequently mentioned by applicants in the VHP process.

We could imagine reduced timelines with authorised medicinal products when these are used within the authorised indication (in-label). In all other cases, for instance, off-label indications of medicinal products we reject any shortening of the timeline. In addition it has to be taken in account that the CAP is meant to be conducted within 60 days, a deadline within which, in many member states, a clinical trial is meant to be assessed nowadays. Owing to the fact that – despite the considerable need for co-ordination for harmonisation purposes within the CAP – the authority's deadline is not supposed to be extended, this would be tantamount to a *de facto* reduction of the assessment deadline. As is already the case today, the deadlines should be correspondingly extended for certain medicinal products such as gene therapy medicinal products or medicinal products containing genetically modified organisms. We cannot support the concept of pure notification procedures without an approval process since these also need to be examined and therefore do not constitute a genuine saving of resources.

Consultation item 8: "Pre-assessment"

The definition of the (objective) criteria of a low-risk, Type A trial, should be more precisely clarified and specified. A classification according to the phase or approval status of the investigational medicinal product or active substance, alone, is not deemed to be sufficient to ensure the safety of the trial subjects and the quality of the trial.

The trials should fulfil both the criteria under a) and those listed under b). Furthermore, it should thereafter not be possible to modify an investigational medicinal product, which is the subject of a Type A trial, in respect of the pharmaceutical quality specified at the time of its marketing authorisation. Moreover, in Type A trials, the investing medicinal product should only be used in accordance with the terms of its marketing authorisation; a use which is in conformity with its indication, alone, is not deemed sufficient since potential risks can emerge just by disregarding contraindications and limits of use.

re: a)

The trial treatment should be a standard treatment and not simply a part of such a treatment. There is a need to discuss whether this can be done in a member state or in the concerned member state or in the majority of member states. At least the latter option should be possible especially since, with 27 member states, a corresponding variance can be assumed.

re: b)

The "insignificant additional risk" in itself and compared with "normal clinical practice" must be more clearly specified and harmonised. In some cases, considerable differences exist among the Member States with regard to assessment in this area, for example, in re-

spect of X-ray examinations.

We consider the conduct of a pre-assessment for this trial type to be useful. However, issues regarding responsibility, deadlines and assessment criteria must be clarified more precisely.

Owing to the national particularities regarding possible medical treatment liability, this pre-assessment cannot be conducted by another member state or by the EMA (or the Commission). It seems acceptable to examine this in the course of the validation by the RMS and to subsequently determine, in agreement with the Concerned Member State, whether the prerequisites for a Type A clinical trial exist. However, in the event of an objection from even one of the Concerned Member States, no Type A classification should be granted and the trial should follow the normal procedure.

Furthermore, we need to specify which additional simplifications, apart from those already contained in the Commission's proposal, are to apply to trials classified as Type A (for example, the labelling of the investigational medicinal product).

2. Improved adaptation to practical requirements and a more harmonised, risk-based approach to the procedural aspects of clinical trials

2.1 Limiting the scope of the Clinical Trials Directive

2.1.1 Enlarging the definition of "non-interventional" trials

Consultation item 9: "Non interventional trials"

The Federal Institute for Drugs and Medical Devices *(BfArM)* and the Paul Ehrlich Institute *(PEI)* agree with the Commission's proposal that the definition of non-interventional trials (NIS) should be left as it is. In other words, the prerequisite remains that investigational medicinal products may only be utilised within the scope of the terms of their authorisation and the use, diagnosis and monitoring may only proceed according to normal clinical practice. This means that no additional treatment/diagnosis and no randomisation or additional interventions will be conducted as a result of specifications laid down in a protocol.

In principle, we support the Commission's approach to elaborate and harmonise the interpretation of the definition, as well as the requirements to be met by these trials, appropriately and in a manner which meets legal standards, in other words, in a manner which is in conformity with existing legislation and regulations.

2.1.2 "Excluding clinical trials by 'academic/non-commercial sponsors' from the scope of the Clinical Trials Directive"

Consultation item 10: "academic/non-commercial sponsors"

The Federal Institute for Drugs and Medical Devices *(BfArM)* and the Paul Ehrlich Institute *(PEI)* are in full agreement with the Commission in that the assessment of a clinical trial, as well as the assessment procedure and the requirements, must be independent of the applicant's status.

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

The well-known problems in the area of safety reporting are based less on what is possibly a too complex regulation, and more on the lack of willingness or the inability of sponsors and investigators to conduct adequate assessments of safety alerts before report-

ing them. In this instance, some degree of harmonisation, or at least training by the sponsors in the interpretation and implementation of relevant guidelines, for example, the various ICH E guidelines or the GCP guidelines could be indicated. As long as the non-observance of international guidelines on the reporting of safety incidents has no consequences for investigators and sponsors, the quality – especially that of the SUSAR notifications – is not likely to improve.

Even though, in principle, the Commission's evaluation is sensible, it care should be taken that no risk-based reduction in quality develops in the area of safety reporting. The principles of good clinical practice are to be applied at all times. Certain interpretation aids could, if necessary, be addressed in corresponding 'Question & Answer' papers by the CTFG or the Commission. It should be mentioned that a risk-adapted dossier (IMPD) already exists in the form of a simplified IMPD for investigational medicinal products which already possess a marketing authorisation for the EU/EEA.

Consultation item 11: "risk adapted rules defined by commission ...in Annexes to CTD, e.g. CT1, CT2, CT3"

The Federal Institute for Drugs and Medical Devices *(BfArM)* and the Paul Ehrlich Institute *(PEI)* support the harmonisation process. However, this should be pursued primarily on the basis of Directive 2001/20/EC and not on the basis of guidance documents; we consequently do not support this proposal by the Commission.

Owing to the fact that national responsibility and the responsibility for monitoring the risk entailed in the clinical trial lie with the national authorities, and given that national differences exist, *inter alia*, with respect to treatment standards, the centralisation of a risk-based approach by means of guidance documents from the Commission strikes us as highly problematic. If desired, such an approach could then also be enshrined in Directive 2001/20/EC, whereby it should be taken into account that the requirements in respect of safety and quality should be, in principle, the same in all studies and independent of the sponsor's status and of the supposed risk.

Experience with revisions of the existing Guidance Documents by the Commission, to date, in which the essential points of criticism and also the expertise of the Member States were disregarded, in some cases, has proven that a pure consultation procedure is not ideal when dealing with risk assessment. If we were to further expand the current consultation procedure as well as the guidance powers of the Commission, it would mean, in the final analysis, that the Commission would be deciding which risk the Member States will be facing. We therefore urgently propose that Guidance Documents are only adopted in agreement with the Member States or by means of a qualified majority vote. The harmonisation of the approval and monitoring of clinical trials should continue to be the task of the CTFG which has been commissioned for this purpose by the HMA.

Consultation item 12: "other key aspects on which more detailed rules are needed"

As already remarked, it are precisely the key aspects which should, in principle, be enshrined in the Directive; technical standards are sufficiently described in the ICH standards. Consequently, we see no need for additional guidance documents from the Commission.

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

Consultation item 13: "auxiliary medicinal products, AMP"

The Federal Institute for Drugs and Medical Devices *(BfArM)* and the Paul Ehrlich

Institute *(PEI)* think it necessary to replace the current ambiguity surrounding the term 'non-investigational medicinal product' (NIMP) by introducing and defining a new term.

The clarification of the definition of an investing medicinal product (IMP) is welcomed and accepted. The definition of "auxiliary medicinal products" is problematic in that it might not yet cover challenge agents since these are not necessarily medicinal products. It would therefore be more appropriate to speak of an "auxiliary product" which should then include provocation substances and diagnostic medicinal products as well as medical devices which do not have a CE marking.

Rules governing investigational medicinal products (IMPs) and "auxiliary [medicinal] products" should be identical, where possible. Particularly with respect to their quality, a safe and GMP-compliant manufacturing process should be guaranteed especially where active (pharmaceutical) ingredients are concerned.

Furthermore, it must be ensured that safety alerts regarding auxiliary [medicinal] products can be reported regardless of their authorisation or other regulatory status. We wish to point out that, at the present time, only safety alerts which concern a medicinal product – the Business Rules go as far as to envisage only those concerning investigational medicinal products (IMPs) – can be reported to the European pharmacovigilance database 'Eudra-Vigilance'. Electronic reporting is therefore not possible without a reference to a medicinal product.

2.4 "Insurance/indemnisation"

Consultation item 14: "insurance/indemnisation"

Here too, the question arises as to how to define a 'low-risk trial' and who is responsible for the evaluation. In Germany, this task is incumbent on the Ethics Committee. The amount and scope of the special insurance which has to be taken out for clinical trial subjects in Germany is determined by the size of the risk. Nonetheless, an exemption for low-risk clinical trials which accompany a course of treatment strikes us as appropriate. These are clinical trials in which only medicines authorised for marketing in Germany are used as investigational medicinal products, under in-label conditions, and where trial-related measures involve minimal burden and risks for the trial subjects. We welcome the use of risk-adapted insurance policies. In addition, competition in the European insurance sector should be improved so as to be able to offset the differences pointed out in Section 7.2 of the Commission Paper.

2.5 "Single sponsor"

Consultation item 15: "single sponsor"

The Federal Institute for Drugs and Medical Devices *(BfArM)* and the Paul Ehrlich Institute *(PEI)* explicitly support the retention of the concept of a 'single sponsor' in Europe. The concept of 'divided' sponsor responsibilities (regardless of the way in which they are divided) is not convincing. There is a risk here that the responsibility structures are no longer clearly defined and no longer transparent. A sponsor is supposed to take responsibility for GCP-compliance. It should also be mentioned that liability law is not harmonised throughout Europe.

2.6 "Emergency clinical trials"

Consultation item 16: "emergency clinical trials"

We support European harmonisation. The Commission's proposal seems appropriate and fulfils the provisions contained in Section 41, sub-section 2, sentence 2 of the Federal Act on Medicinal Products. Nevertheless, we should also consider what is to be done with

the data already collected should the subject refuse to participate when his/her emergency situation no longer exists.

3. Ensuring compliance with Good Clinical Practices in clinical trials carried out in third countries

Consultation item 17: "GCP in CT in 3rd countries"

Clinical trials conducted in third countries require a confirmation that they comply with the Statement of GCP-Compliance pursuant to ICH E6. The entry of the clinical trial into a public trial register is not considered to be absolutely necessary, especially since Phase I trials constitute intellectual property and as such are not entered into the European Union's clinical trials register. Only trials which were or are conducted in Europe should be registered in the European Clinical Trials database (EudraCT). Studies conducted in third countries should not be registered there unless they were/are also conducted on the territory of a member state of the EU/EEA. An entry in an international trial register, for example, that of WHO, is considered acceptable. We wish to suggest that registry entries contain information as to whether the trials were conducted in conformity with ICH GCP, whether a positive opinion from the Ethics Committee had been received and whether the trial was conducted in compliance with the Helsinki declaration.