

**Comment by the Federal Institute for Drugs and Medical Devices
in coordination with the
Paul Ehrlich Institute and the
Federal Ministry of Health**

on

the public consultation¹

**ASSESSMENT OF THE FUNCTIONING OF THE
'CLINICAL TRIALS DIRECTIVE' 2001/20/EC**

The Federal Institute for Drugs and Medical Devices, the Paul Ehrlich Institute and the Federal Ministry of Health appreciate the consultation and the subsequent discussion process and they would like to thank the Commission for having the opportunity to comment on the aforesaid public consultation.

We agree with the view of the Commission that clinical trials are an indispensable part of clinical research and that medical treatment is being further developed and improved. In its analysis the Commission starts out from 4,000 to 5,000² studies each year in the EU, of which approximately 64% are sponsored by pharmaceutical industry and 36% by non-commercial sponsors³. According to estimates of the Commission, only 60 - 80% of the trials are intended to be used in the framework of marketing authorisation applications, and (only!) 25% of clinical trials are performed in more than one EU Member State⁴.

Approximately 1,100 - 1,200 trials per year are authorised by the Federal Institute for Drugs and Medical Devices, and about 150 – 200 trials by the Paul Ehrlich Institute. Thus it can be started out from the assumption that Germany takes part in approximately 25 – 30 % of all clinical trials carried out in Europe.

From the German point of view, there is consent to the statement of the Commission that the 'Clinical Trials Directive' (Directive 2001/20/EC of the European Parliament and of the Council of 4 April on the approximation of laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use) has brought about considerable improve-

¹ http://ec.europa.eu/enterprise/pharmaceuticals/clinicaltrials/docs/2009_10_09_public-consultation-paper.pdf

² The text of the draft paper mentions 4.000-6.000 trials per year (page 4), table 1 on page 5 provides the concrete figures for each year: 991(2004) to 5028 (2007)

³ page 5 of the draft paper

⁴ page 6 of the draft paper

ments in the safety and reliability of data generated in clinical trials. It is also true that this Directive has considerably improved the co-operation between the national authorities competent for the marketing authorisation. However, whether it is justified to criticise the Directive, e.g. for having led to the declining attractiveness of a patient-oriented research, has to be thoroughly analysed on our part. After all, the Commission itself states (report from the Stoiber Group⁵, Impact on Clinical Research of European Legislation Report⁶) that except for one single case, research has not been considerably impaired in the individual Member States, even if the implementation of clinical trials has become more difficult and more expensive.

Doubtlessly, according to the GCP-standards, clinical trials are more expensive than the former studies. Costs arise from the preparation of trial protocols as well as from the evaluation of applications by the ethics committees and authorities, and also for the insurance. Considerable funds have been spent on the implementation of the Directive, which partly also have to be raised by sponsors involved in clinical trials. Significant efforts have been made to create qualified facilities for clinical trials also at the universities, and to recruit and train suitable staff. Consequently, many universities today can use qualified testing facilities for the purpose of study planning, filing of applications, implementation and assessment as well as for the purpose of monitoring and meeting their obligations to report. As a whole, the rise in the costs involved are accompanied by an obviously better quality of the studies submitted.

In the following the consultation paper mentions the Key Issues and strategies from the Commission's point of view. The continuous conclusion is that no real harmonisation has been achieved in the Member States. However, the Commission does not mention that Article 3 of the Directive grants a right to the Member States to issue more extensive safeguard provisions (as Germany has done e.g. in the case of minors⁷). In addition, the different diagnostic, medical and therapeutic standards in the Member States are not mentioned which, in our opinion, may well be the reason for diverging evaluations.

In several contexts the consultation paper suggests to transfer the assessment to other Member States, and even proposes a procedure of central marketing authorisations for clinical trials at the European Agency for the Evaluation of Medicinal Products (EMA). We cannot agree to these ideas and therefore object to them. Hereinafter, you will find further explana-

⁵ http://ec.europa.eu/enterprise/policies/better-regulation/files/hlg_opinion_pharma_050309_en.pdf

⁶ <http://www.efgcp.be/icrel/>

⁷ Article 3: 1. "This Directive shall apply without prejudice to the national provisions on the protection of clinical trial subjects if they are more comprehensive than the provisions of this Directive and consistent with the procedures and time-scales specified therein."

tions in detail.

KEY ISSUE N°1 TO BE ADDRESSED:

MULTIPLE AND DIVERGENT ASSESSMENTS OF CLINICAL TRIALS⁸

In this context, the Commission basically criticises the multiple marketing authorisation procedures in the various Member States. Further to higher costs, bureaucratic burden and diverging evaluations, an increased period of time needed and a difference in starting the clinical trial in the various Member States are mentioned.

It is true that one of the possible solutions mentioned there is the Voluntary Harmonisation Procedure (VHP⁹) of the Clinical Trials Facilitation Group (CTFG), but this is not specified in the following. We hold the view that the Voluntary Harmonised Procedure and/or its further development holds a lot of potential for an efficient standardisation of the implementation of the Directive. This voluntary cooperation should therefore be supported, and the Voluntary Harmonisation Procedure should be extended.

Under paragraph 3.3.2.1¹⁰ the Commission suggests two procedures with different extent: Option (a) corresponds to the principle of the decentralised procedure/mutual recognition procedure for marketing authorisations and requests a common opinion of all national competent authorities participating (NCA¹¹). The assessment is supposed to be done only by a 'Reference Member State' (RMS), the 'Concerned Member State' (CMS) has merely an advisory function, and in case of diverging opinions, clear decision-making procedures will have to be established. Option (b) corresponds to a central procedure to be performed at the EMEA, and in this context, the connection / continuum between clinical trials and the (central) marketing authorisation is considered to be an advantage.

A centralisation of the authorisation process and the central assessment of clinical trials definitely have to be objected to. There are several reasons for this:

- In case of a damage, shifting the responsibility to one Member State or to the EMA, as it had been proposed, will be hard to convey to the general public. This was already proved in the public discussion after the clinical trial participants had fallen ill from the test drug "TeGenero "1412" in a life-threatening manner. However, every Member State

⁸ page 12 of the draft paper

⁹ Voluntary Harmonisation Procedure (VHP): Voluntary procedure of the CTFG for a joint assessment of an application without essentially extending the authorisation procedure

¹⁰ page 15 of the draft paper

¹¹ NCA National Competent Authority

shall be at liberty to implicitly authorise clinical trials, to consent to the positive assessment of another Member State or to participate in a Voluntary Harmonisation Procedure.

- Both options suggested would give the applicant the opportunity of changing primarily mono-national trials which would possibly be rejected or modified by the national licensing authority, into a multi-national trial by participation of one singular centre abroad and consequently undermining the objections of the lead licensing authority (in the territory of which the majority of the patients is still included). In Germany, this method has already been observed, and we call it "Ethics Committee-hopping" (change of the head of the clinical trial following the rejection by his Ethics Committee and subsequent approval by another Ethics Committee). If a mutual recognition procedure or a central procedure were to be applied, it would have to be ensured in any case that all Member States in the territory of which a larger number of patients shall be included, will be able to do a reasonable assessment. As a consequence of the participation of another Member State, they shall not be urged to assume the role of a Concerned Member State which is hardly able to raise objections any more.

As far as the role of the Ethics Committees is concerned, the national competence of the Member States is (still) being accepted by the Commission. In the paper it is proposed to reduce overlaps between the Ethics Committee and the National Competent Authorities and to improve their co-operation. The European co-operation of the Ethics Committees is to be improved, e.g. by the development of networks. It is suggested to envisage a joint submission ("one-stop shop") of applications to the competent authorities for the marketing authorisation and the Ethics Committees. From the German point of view, the aforesaid last proposal is considered to be useful. A joint application form which is to be submitted electronically to a central agency (at national or European level) could considerably facilitate the submission of applications and their processing and could save costs as well.

KEY ISSUE N°2 TO BE ADDRESSED:

INCONSISTENT IMPLEMENTATION OF THE CLINICAL TRIALS DIRECTIVE¹²

With regard to this aspect, the Commission basically criticizes the differences in implementing the Directive in the individual Member States. The following examples are mentioned:

¹² page 17 of the draft paper

Substantial Amendments:

The Commission holds the view that a large number of substantial amendments is caused by the different interpretations by the individual Member States.

In our opinion, the problem here is the far-reaching definition within the Directive. Germany has transposed the definition included there almost literally into its Ordinance on Good Clinical Practice and keeps to the corresponding EC Directive ENTR/CT1. The judgement as to what is meant by "substantial" provides a margin of discretion which can be interpreted in different ways.

Reporting adverse reactions to the Community database EudraVigilance

The Commission complains about differences in the implementation in the individual Member States. Germany has implemented the reporting system for serious unexpected suspected adverse reactions (SUSAR¹³) in accordance with the Directive and automatically sends its reports from the national database to ***EudraVigilanceCTM***¹⁴. For quite a long time already, there have been efforts on the part of the EMA to introduce a direct notification to the ***Eudra VigilanceCTM*** which is compulsory. From the national point of view, however, a solid work with the current form of ***EudraVigilanceCTM*** is not yet feasible, but only with the national pharmacovigilance database. In our opinion, the 6-fold increase in reports as compared to 2003, which is criticized by the Commission, is first and foremost based on (systematic?) erroneous reports from many sponsors. In this context, adverse reactions are reported which are neither unexpected nor severe, and in many cases they have not even been caused by investigational medicinal products. In those cases, remedial action could be taken by a clarification and by calling the sponsors to account in a stronger manner¹⁵.

From the point of view of the Commission, the reports should be (exclusively) sent to ***EudraVigilanceCTM*** to increase the safety. Yet, it cannot be understood how the safety could be increased by merely changing the channel of reporting. It is true that the data are in only one database, but a sufficient safety assessment is not possible all the same, due to the weakness of the system and the multitude of "erroneous" reports. On the contrary, the monitoring of the reports by the authority competent for the marketing authorisation prior to passing them on to ***EudraVigilanceCTM*** leads to a considerable improvement of the data

¹³ SUSAR-Serious Unexpected Suspected Adverse Reaction

¹⁴ EudraVigilanceCTM — EudraVigilance Clinical Trials Module

¹⁵ If a sponsor does not to make a reasonable assessment of serious adverse events (SAE) and reports every SAE, be it expected or blinded, as a SUSAR, it would be possible to assume deficiencies in the quality systems of such a sponsor and in repeated cases to doubt the implementation in accordance with (ICH) GCP thus having an argument for enforcement.

quality.

In order to avoid the big problem of duplicate reports to EudraVigilance, we hold the view that all reports should bear a code which the sponsor receives from **EudraVigilanceCTM** (similar to the EudraCT number). Then a simultaneous reporting to the national authority and **EudraVigilanceCTM** could be effected without any problem.

Differentiation between non-interventional and clinical trials

The Commission criticizes the different borderlines drawn between non-interventional and clinical trials in the individual Member States.

Whereas most of the Member States favour a risk-based approach, i.e. non-interventional, and possibly also reach their decisions accordingly, the definition included in the Directive does not provide for this approach. Here, the delimitation from clinical trials is exclusively based on the question whether the treatment and monitoring of patients is done in accordance with the marketing authorisation and only in line with good practice of medical care (e.g. no using of blood samples for purposes which do not correspond to the usual practice of medical care). In our opinion, the Directive provides for sufficiently clear provisions on this issue, the compliance of which (merely) has to be ensured by the Member States.

Consequently, a more detailed clarification of this provision is not necessary from our point of view.

In general, the Commission suggests two options for the items set forth under KEY ISSUE N°2:

One of the options suggested there is a clarification of the Directive, which we basically appreciate, except for the delimitation of non-interventional from clinical trials. In order to harmonise the interpretation of "substantial amendments" it would be useful to clarify the provisions of the Directive and, in addition, to give examples in supporting documents. The required reporting of adverse effects could also be optimized by such a clarification of the Directive. When elaborating guidelines, it is of utmost importance to take into account that these are in accordance with the specifications in the Directive.

The second option suggested is readopting the content of the Directive in the form of a Regulation. From our point of view this is not a solution. This option does not relieve the Commission of its obligation to clarify the current phrases, since otherwise even a Regulation will be implemented in different ways. However, if the text of the Directive were sufficiently clear, it would also be possible to transpose it in a harmonised way (with the provision that

national particularities – as thus far admitted in Article 3 of the Directive - will no longer be permitted or will be limited in a stricter and/or clearer manner). As too many circumstances in the field of clinical trials, as e.g. the law concerning liability issues, insurance of healthy volunteers, health insurance, etc. have not been harmonised at European level, we hold the view that a Regulation would not lead to any considerable advantage.

KEY ISSUE N°3 TO BE ADDRESSED:

REGULATORY FRAMEWORK NOT ALWAYS ADAPTED TO THE PRACTICAL REQUIREMENTS¹⁶

With regard to this issue, the Commission states that not all requirements of the Directive and the corresponding guidelines are feasible and justified for every clinical trial. Clinical trials and their risks partially show great differences, e.g. with regard to the patient population, the knowledge about the investigational medicinal product (IMP) or the indication of the IMP (approved indication or not approved) This becomes particularly obvious in the trials sponsored by so-called non-commercial and/or academic sponsors, which are not necessarily implemented for the purpose of obtaining a marketing authorisation. Another example that is given is the responsibility of the sole sponsor of a clinical trial, whose difficult task it is to assume responsibility for the implementation of the clinical trial in other Member States as well. This is a problem the consequences of which are discussed in a basically appropriate manner in the paper of the Commission.

With regard to this problem, the Commission offers three different solutions in its consultation paper:

As a first option it is proposed to review the existing implementing guidelines on clinical trials, so that different levels of requirements are described within their scope, e.g. for the monitoring, the reporting or the labelling of the investigational medicinal products. We explicitly welcome this suggestion, yet we would like to point out that when amending the guidelines it has to be strictly respected that their content is in conformity with the Directive and does not have any deviations as compared to the latter.

A review of the Directive is also mentioned as a second option. This is a proposal which we essentially appreciate.

¹⁶Seite 21 des Konzeptpapiers

The third option that is suggested is to exclude clinical trials of academic sponsors from the scope of the Directive, as a result of which different national regulation would be applied. From our point of view this is not acceptable, under no circumstances. The application of the Directive to all clinical trials has led to a considerable increase in quality and reliability of the trials. This is not just about the fact that clinical trials that are not conducted in line with the Directive could not be used for any future licensing and would thus have to be repeated (and this time in conformity with the Directive). Over and beyond that, a repeat of the clinical trial for licensing purposes would not be justifiable for ethical reasons. The patients' safety is paramount, so that academic trials may not be subject to different standards than commercial trials.

KEY ISSUE N°4 TO BE ADDRESSED:

ADAPTATION TO PECULIARITIES IN TRIAL PARTICIPANTS AND TRIAL DESIGN¹⁷

This issue deals with special cases of clinical trials. Thus, for example, peculiarities of "paediatric clinical trials" and trials in emergency situations where it is not feasible to obtain informed consent, are described. There are substantial differences between the national standards in this field. It has to be pointed out that the German legislator had already adopted corresponding regulations prior to the elaboration of this Directive and that furthermore, the Directive has been implemented in Germany in such a manner that both types of clinical trial on principle do not constitute a problem. However, certain fundamental restrictions are applicable for children in Germany, and they have been intended by politicians: Healthy minors shall not participate in clinical trials if there is no individual benefit for the participating healthy child (Section 40 paragraph 4 of the German Medicinal Products Act).

The Commission suggests an adaptation of the Directive, an option which we appreciate.

KEY ISSUE N°5 TO BE ADDRESSED:

ENSURING COMPLIANCE WITH GOOD CLINICAL PRACTICES ("GCP") IN CLINICAL TRIALS PERFORMED IN THIRD COUNTRIES¹⁸

Approximately 25% of the clinical trials are implemented in at least one other non-European third country. 65% of all clinical trials for obtaining marketing authorisations in central authorisation procedures include data from third countries. In this context, the consultation paper discusses, *inter alia*, the role of third, non-OECD countries and the advantages and disadvantages of corresponding trials. The Commission fears that due to an increasing im-

¹⁷ page 24 of the draft paper

¹⁸ page 27 of the draft paper

plementation of clinical trials in non-OECD third countries, the risk of clinical trials that do not comply with Good Clinical Practice (and/or do not comply with the Directive) will grow. The Commission proposes several measures for a possible reduction of this risk. We largely agree to the judgement of the Commission. As a rule, these suggestions are useful, but in their entirety, maybe not all of them can be implemented.