ASSESSMENT OF DIRECTIVE 20/2001/EC
OPEN CONSULTATION OF THE EUROPEAN COMMISSION

REPLY OF THE HUNGARIAN HEALTH ADMINISTRATION

General considerations

Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the 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 (hereinafter referred to as the CTD) has brought about significant progress in respect of establishing single requirements on clinical trials. As the consultation paper of the European Commission asserts, the CTD increased the health protection of trial subjects as well as the reliability and availability of clinical data.

The Hungarian Government attaches utmost importance to the clinical trials not only from pharmaceutical R&D but also from a broader public health perspective, since the studies facilitate the patients' access to certain therapies which represent the only possible way of their treatment. It is also evident for us that due to clinical investigations our physicians gain important skills that are crucial for their professional progress and, after all, for the improvement of the healthcare system. In addition, the "clinical investigation market" represents important added value for the industry sectors involved, since it allows for free technology transfer, new quality assurance approach and it is also integrates actors in the international collaboration.

In this respect, the Hungarian Government is particularly concerned about the recent decline of clinical trials in the European Union. We can therefore easily subscribe to the need for revising, from the above described perspective, the specific administrative practices and, if necessary, the regulatory framework.

Although the document mentions relevant problems, we are of the position that is should be examined in each case whether the solutions necessarily require legislative measures. In our views, legislation should be used as an ultimate tool when implementing environment of the current legislative framework can not be improved any more in order for the elimination of barriers to clinical trials.

Having regard to the fact that most of the problems identified in relation with implementation of the CTD, it is indispensable to assess if, by means of more instructive interpretation tools (guidelines) and a better use of the current cooperation mechanisms, it is feasible to improve the current situation and avoid legislative revision.

Our responses to the consultation questions have been formulated in line with the above-mentioned considerations.

Consultation item n°1: Can you give examples for an improved protection? Are you aware of studies/data showing the benefits of Clinical Trials Directive?

The protection of trial subjects, the weight of ethical opinions, the need for reliable clinical data and the simplification of the administrative procedures were taken into account in the

course of the adoption of the CTD. We share the view that the entry into force of CTD resulted in the increased safety of trial subjects, as well as more unified and accountable authorisation procedures. However, we also agree with the criticism that the administrative costs have seriously affected the competitiveness of conducting trials in the EU.

It is therefore necessary to examine how a realistic and sustainable balance can be established between the achievements of the CTD and the need for better encouragement of clinical trials.

Consultation item n°2: Is this an accurate description of the situation? What is your appraisal of the situation?

The conclusions of the document at this point are correct. According to our experiences, the specific member state authorities and ethics committees use different standards. It is not rare that in the course of the authorization procedure of a multi Member State clinical trial, one of the ethics committees or competent authorities ask about something which has already been adequately answered in another Member State, or national authorities ask different questions. Such additional requirements substantially delay the start of the trial and cause extra administrative burden both for the sponsors or the authorities. Differing national requirements may also determine the geographical distribution of clinical trials and the establishment of study protocols. If documenting obligations or evaluations vary from one Member State to another, there might be cases when some Member States fall outside the potential clinical trial sites.

In our view, a possible solution could be a mechanism allowing for the peer review of the evaluations as it already has been established in the case of marketing authorisation procedures of medicines.

Consultation item n°3: Is this an accurate description? Can you quantify the impacts? Are there other examples for consequences?

Regretfully, weaknesses mentioned in the document exist and need solutions. Different requirements set up by the specific Member States and the existence of parallel authorisation procedures multiply the workload on the experts and the administrative staff and increase the costs of authorization process without adding any further significant professional and safety value.

As far as the delay of “first patient in” is concerned, it must be seen that Member States are in a concurring situation since sponsors do not necessarily wait for the closure of each national procedure before they start recruiting trial subjects. If they are granted an authorization in one Member State, the sponsors start the recruitment, which means that patients from “slower” Member States may fall outside the trial and therefore get deprived of therapies under investigation which may be the only way of their survival or recovery.

Consultation item n°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?

Firstly, it should be examined that the Voluntary Harmonization Procedure (VHP) can be made more efficient and smoother, in order that it ensures timely decision making.

As far as the option on application of reference authorities is concerned, it is questionable how time limits can be observed if opinion from the reference authority was evaluated at a later stage by the other authorities. On the other hand, we appreciate that this solution can lead to a simplified procedure and that the national authorities could compete for the *reference* status, which is beneficial for the quality and rapidity of the authorisation process.

The third option envisaging authorisations that are valid for the whole EU would require a regulation where no further, and possibly diverging, national implementation measures are necessary and by which national adaptation problems could be avoided. The consultation document does not go into details concerning documents to be provided in national languages, the assessment of which should remain at national level. The centralized procedure needs some reflection from SME perspective as well, since this scheme can be burdensome for small and medium enterprises. It is also to be assessed whether the centralized procedure can facilitate the timely start of investigations. Notwithstanding the above mentioned, we can support this option.

In our view, any procedure should confine with the max 60-day-deadline. The transparency of authorisation procedures could also be ensured by simplified procedural rules and clearer evaluation criteria. In case of clinical trials conducted only in one Member State, the national authorisation schemes should be maintained while the evaluation criteria should be equivalent to the EU rules.

Consultation item n°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?

We are in favour of strengthening networks of national ethics committees. The consultation document, however, does not give sufficient information on the advantages and disadvantages of each option. For example it does not mention the benefits of the decentralization of ethical assessments in case of multinational clinical trials. The endeavour of clarifying the respective scopes of assessment by national competent authorities and ethics committees is welcome. Hungary agrees that parallelism and overlaps should be minimised. We note that in Hungary the request for authorisation of a clinical trial is assessed in a “one-stop shop” system, which works very well and efficiently, and we can recommend it to the other member states.

Consultation item n°6: Is this an accurate description of the situation? Can you give other examples?

The description is accurate. We agree that the definitions mentioned in the document should be refined. The differing interpretations of SAE and SUSAR in the Member States make confusion resulting in an undue number of notifications. In the course of amending SAE and SUSAR definitions, they should be adjusted to the risks and technologies relevant in the 21st century. The fine tuning of the relevant ICH GCP standard should also be considered.

Consultation item n°7: Is this an accurate description? Can you quantify the impacts? Are there other examples for consequences?

We agree with the description. The current system of SUSAR increases risks instead of having added value. At the same time, it generates unnecessary costs for all parties involved (authorities, ethics committee, companies and clinical site), and eventually makes the

medicinal product more expensive. In addition, non-commercial sponsors can hardly fulfil the current conditions.

Consultation item n°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?

Each option has advantages and disadvantages. It should be, however, considered whether the problems that occurred in connection with the application of the Directive can only be solved with regulatory means. We believe that – besides the revision of the legislation – the shortcomings of the implementation of the Directive should also be identified and examined if they can be solved by non-legislative means, possibly in the form of soft law. We are not against, however, a new legislative concept, if its necessity is justified.

Consultation item n°9: Can you give examples for an insufficient risk-differentiation? How should this be addressed?

We agree that the requirements should align with the risks of the clinical trial. Subject to the characteristics of the clinical trial, a differentiated approach should be introduced. At the same time, the legislative acts or guidelines, as appropriate, should lay down adequate requirements for each phase of the clinical trial. For example phase I and phase IV trials differ from each other in such an extent, that it is reasonable to assess them along differing considerations.

Consultation item n°10: Do you agree with this description? Can you give other examples?

Though the concept of "one single sponsor per clinical trial" can create practical difficulties, we are in favour of it, since the concept of "multiple sponsors" may result in the unnecessary fragmentation of responsibility.

Consultation item n°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 this problem?

Consultation item n°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?

Common answer for consultation items n°11 and n°12:

If the Directive is amended, it should be considered whether current soft law rules need to be included to the Directive or these rules and elements should stay in the form of guidelines. Those rules, which should be continuously adapted to the changing circumstances, should be regulated in the form of soft law, while incorporating the more stable ones to the Directive. The current guidelines can also be further clarified.

Consultation item n°13: Would you agree to this option and if so what would be the impact?

We are not in favour of the exclusion of academic sponsors from the scope of the Directive; since it risks that commercial sponsors will carry out "false academic trials" in order to avoid stricter applicable rules. Instead of excluding academic sponsors from the scope of the Directive, we suggest that academic clinical trials are facilitated by various means.

Consultation item n°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?

The current legislation of clinical research for paediatric medicines is appropriate. These trials are unpopular because of personal and financial reasons, instead of legislative shortcomings. A solution could be to shorten deadline of the procedure of authorisation.

The Directive incorporates sufficient safety rules and safeguards in terms of children. On the other hand the cooperation could be improved between the competent authorities (which are in charge of the authorisation of clinical trials) and the Paediatric Committee (set up by Regulation 1901/2006/EC).

Consultation item n°15: Should this issue be addressed? What 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?

We support that emergency clinical trials are addressed by introducing common EU standards. Shortening the documentation size should be considered in order for the patient – if he/she has the capacity to act – to get the information about the clinical trial as soon as possible.

Consultation item n°16: Please comment? Do you have additional information, including quantitative information and data?

The term "third country" used in the consultation document refers to a very heterogeneous group of countries. These countries have very different practices (e.g. regarding patient involvement, data quality, adherence to the ethical aspects) in terms of clinical trials; they should not be treated and described uniformly. We agree that special emphasis should be laid on the supervision and enforcement of international rules for the protection of clinical trial participants. Cooperation between national competent authorities should be improved in order to be ensured that they carry out mutually recognized GCP inspections in third countries.

Consultation item n°17: What other options could be considered, taking into account the legal and practical limitations?

The introduction of a "black list" should be considered. There is a "black list" used in the USA for clinical investigators and clinical sites, and EudraCT created the grounds of a similar tool in Europe. On these models a "third country black list" could be set up.

Consultation item n°18: What other aspect 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?

Due to their lack of capacity to ensure GCP conformity, small and medium sized enterprises are often not able to carry out clinical trials in third countries. New regulatory solutions are needed in order that SMEs are able to make use of the benefits of clinical trials carried out in third countries without loosening safety and ethical requirements.

Budapest, 8 January 2010