CONSOLIDATED COMMENTS OF THE CLINICAL TRIALS FACILITATION GROUP (CTFG) ON THE ASSESSMENT OF THE FUNCTIONING OF THE "CLINICAL TRIALS DIRECTIVE" 2001/20/EC ENTR/F/2/SF D(2009) 32674

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1.1. General Comments:

The Clinical Trials Facilitation Group (CTFG) appreciates the initiative of the EU- Commission to measure the impact of the CLINICAL TRIALS DIRECTIVE" 2001/20/EC (CTD) in Europe. The CTFG is pleased to join this process as a HMA working party and would like to offer its support of measurements of the development of clinical trials (CT) in Europe. In this respect very important information on the development of CT has been given by the commission in the first part of the consultation paper. The CTFG would appreciate if this information could be collected regularly and if the CTFG could receive this information, too

In the first part of the consultation paper the procedures during the approval and performing of CT as well as numbers on the development of CTs are given.

The numbers given under the chapter Background (2.1.) and the description of the process of Clinical Trial Approvals under the chapters 2.2 to 2.4 are generally endorsed. The numbers of staff of the national competent authorities (NCA) given under 2.4 are partially not accurate. In order to give accurate numbers of internal personnel of the NCAs and external

experts involved in CT assessment to the EU Commission and to the public, the HMA might consider requesting the CTFG for new numbers reflecting recent changes.
The Chapter *Achievements but also shortcomings* (2.5) is the only chapter which addresses improvements after the introduction of the CTD. It is only generally stated that the protection of participants and the reliability of data of CT has been improved. It is stated too, that the collaboration of NCAs has greatly improved.
Aside from these general statements the topics improved patients safety and increased reliability of data of CT are considered underrepresented in the document of the EU-Commission. This deficiency is important as these topics are the indispensible basis for the other parts of the consultation document in topics as for example increased administrative burden "without added value", increases of personnel in sponsors organisations, safety reporting, and numbers of CT, especially for non-commercial sponsors, etc.

1.2. 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?

According to the CTFG's opinion the main areas of improved protection of patients derive from:

- Protection of vulnerable populations (CT in children, persons not able to give informed consent, etc)
- Increased patients safety due to the introduction/increase of monitoring/assessment to ensure for example correct dosing, correct inclusion/exclusion criteria , follow up measures, emergency measures, patient information/consent
- Assessment of the quality and toxicology of the investigational medicinal products in a CT
- Increased patients safety by assessing Suspected Unexpected Serious Adverse Reaction (SUSAR) and Annual Safety Reports (ASR) by the NCA and safety measure thereafter
- Alerts of Member States on prohibitions and interruptions of CT as well as of withdrawals of CT applications through the 2 databases
- Introduction of insurances
- Improvement of the data and reliability of CT–results as the basis of treatment decision development
- Inspection of CTs

Before the implementation of the CTD a significant proportion of the CT were performed without the necessary adherence to the above mentioned points. Adherence to most of these points can be ensured today by the raising of grounds for non-acceptance by the NCAs during the application period and the change of the respective part of the documentation by the sponsor. Many thousands of these modified and improved CT were approved in the end.
Finally, even if the numbers of rejections of CT by NCA are low (<1% of the 40000 CT-applications for reasons of safety or quality of IMPs), also this number reflects the efforts of the NCA to ensure the safety of the participants of clinical trials. It is a clear benefit of the CTD that several hundred CTs of poor quality were prohibited in Europe over the last 5 years.

In the next paragraphs the EU-Commission reports of widespread criticism that the Clinical Trials Directive led to a significant decline of the attractiveness of patient-oriented research and related studies in the EU, which greatly reduced competitiveness and further led to an increase in bureaucracy and costs. Furthermore the reports of the comprehensive study on "Impact on Clinical Research of European Legislation" (ICREL) is cited that

- with the exception of one Member State, there has been no decrease in clinical research activity in the EU;

- performing clinical trials, on the other hand, has become considerably more difficult and costly.

1.3. KEY ISSUE N°1 addresses: MULTIPLE AND DIVERGENT ASSESSMENTS OF CLINICAL TRIALS

It is summarised that the CTD aims at harmonising of the regulatory framework for CTs, which is especially important for multinational CTs. The requirements for CTs would be applied differently in the Member States. Although divergent decisions between Member States are very few, sponsors of multinational CT have to respond to varying request of the Member States during the national procedures. Ethics Committees and Competent Authorities assess the Clinical Trial Application independently, by this adding to the complication of the authorisation.

1.4. Consultation item n°2 asks:

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

The CTFG would like to acknowledge the partial multiplicity of the sponsor's efforts to gain an authorisation for a multinational CT. These efforts are increasing with the number of participating Member States (MS). Only 25% of all CT in Europe are performed in more than one MS,: only 10% of the CTs are performed in more than 4 Member States. For these cases the CTFG offers with the Voluntary Harmonisation Procedure (VHP) a mean to reduce the efforts of multiple applications.
In general the procedure of the assessment by the Ethics Committees and by the Competent Authorities works well and without divergent decisions. Divergent decision between the MS are extremely rare (> 0,1 % per year). Efforts to further clarify the different tasks of assessments by Ethics Committees and Competent Authorities are endorsed by the CTFG, as it also noted that the distribution of responsibilities between EC and CA may be variable from member state to member state.

The next chapter concentrates on weaknesses originated by multiple and divergent assessments.

1. First point is the appraisal according the ICREL survey that "the administrative costs for clinical trials, and thus clinical research, increased without added value". It is reported that the administrative cost for receiving a CT approval have doubled since the introduction of the CTD.
2. In the second point it is assumed that a patchwork of separate assessment by the various MS does not necessarily ensure the highest-possible standard of the assessment, as the necessary specific expertise might not always be readily available.
3. The third point proposes that an inconsistent approach lead to longer delays in the inclusion of patients (i.e. first patient in). Furthermore by this, patients would not have access to new innovative treatments.
4. NCA would not use their resources efficiently by doing multiple assessments.

1.5. Consultation item n°3

requires answers to the following questions: Is this an accurate description? Can you quantify the impacts? Are there other examples for consequences?

From the CTFGs point of view this description is far away from being accurate or balanced.

Point 1: The "added value" is the improvement in patient's safety and the reliability of results as the basis for further treatments of patients (see items 1.2).
The basis of the calculation of the doubling of costs is a situation, where in many Member States many areas of CTs were neither regulated, nor reviewed at all or with minimal re-

quirements. This means that any introduction of regulations in a previously weakly regulated field has to increase administrative cost and personnel significantly. Important parts of a CT-Application like the protocol or the investigators brochure were required before the CTD, but have now often improved in quality. Other parts like the quality dossier of the medicinal product (IMPD) were often not required before the CTD, but increase the safety significantly in the case of medicinal products without a marketing authorisation. IMPs with a marketing authorisation do not need an IMPD. Very often the tremendous cost of monitoring or insurances, which are outside the remits of the Competent Authorities, are mixed with cost caused by requirements of the Competent Authorities during a CT-Application.

Point 2: The highest-possible standard of the assessment has to be assured in all clinical trials, not only multi-national CTs. For 75% of the CTs in Europe an authorisation is only requested in one MS. It is therefore not understood, why in the multi-national situation a "patchwork" of assessments "goes to the detriment of safety of the clinical trial participants", whereas in the 75% CTs, in which "the necessary specific expertise might not always be readily available", a single assessment is acceptable. To think the proposal of the second bullet point out, every CT should be assessed in a centralised approach to include all expertise.

Point 3: The date of the inclusion of the first patient in an CT is influenced by many factors.

- Most sponsors do not immediately include the first patient after having received a positive feed-back from both Ethics Committees and Competent Authorities. This is influenced by problems in the recruitment of test centres, contracts, supply of IMP; or orphan indications with few patients etc.
- The numbers given by ICREL do not reflect the time between the approval of the CT and the start of the CT, but the time from the application (in the document incorrectly named "finalisation of the protocol", which is even before an application) and the inclusion of the first patient. For example, times of invalid applications, reaction times to answer grounds for non-acceptance, different application times to the EC and Competent Authorities, different assessment times foreseen by the directive (biologicals, gene transfer products or genetically modified organisms) and recruitment problems in orphan indications with very few patients are part of the 152 days, which are said to be needed in average. In contradiction to a raise of 90% and resulting in 152 days needed for the "first patient in", the same ICREL report states that the average time for an approval of a clinical trial has been declined from an average 60 days in 2003 (before the CTD) to 50 days in 2007(page 77 of the IRCEL report) for the Competent Authorities. The averages for Ethics Committees were about 40 days in 2003 and 2007. The CFTG concludes that any increase in the time to include the first patient does not result from the work of the CA and the EC.
- It is accepted that new and innovative, but also only safe and effective treatments should be provided to the patients as soon as possible. Therefore it is a pre-requisite that the safety and efficacy of the IMPs have been proven in CTs before patients are treated with these medicinal products. Speed has to stand back for the proof of safety and efficacy. Subjects participating in clinical trials do not receive "new and innovative treatments", but experimental substances which are hoped to show an improvement over current accepted treatment. It can only be demonstrated retrospectively whether or not subjects benefited from exposure to these substances.
- The statement that "NCA would not use their resources efficiently by doing multiple assessments" is not shared. It is one of the tasks of the NCAs to ensure the safety of participants and efficacy of IMP by aligning the protocol to the standards of treatments in their countries. By informing the other MS about their positive assessments (EudraCT) or rejections (EudraCT-alerts) the "highest-possible standard of the assessment" and safety for the participants, as requested under bullet point 2, is ensured.
  The NCAs are asked from the patients, political institutions and media for their opinions on clinical trial performed on their territory. These questions can only be answered after the NCA has assessed a clinical trial. Furthermore a structure of independent assessment within the NCA has to be in place, as 75% of CT are performed in single MS only.

The next chapter addresses possible changes of the authorisation procedures in which CT are approved by NCAs

Three general options are named: the Voluntary Harmonisation Procedure (VHP), a decentralised procedure or mutual recognition procedure (DCP/MRP) and a centralised procedure.

The descriptions of the three options are not without bias. Whereas the VHP is only rudimentarily described with a focus on "voluntarily" and "without the involvement of the Commission or the Community legislator", implicating some sort of unreliability, broad attention is given to the other two options, especially the centralised procedure.

1.6. Consultation item n°4

requires answers to the following questions: 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?

Option 1, the Voluntary Harmonisation Procedure has proven to be a successful mean to achieve many features of the other options. It offers already today a one-stop shop, solely electronic submission, one single CTA dossier, a simultaneous assessment of CT by all concerned MS in short time frames, consolidated lists of grounds for non-acceptance, a unique final position by all the MS concerned, flexibility for unseen problems, and in the near future (January 2010) deletion of the VHP Phase 1 (saving up to 4 weeks for applicants), enlargement of its scope and addition of Substantial Amendments. In the last year the VHP has been modified several times to simplify the process for applicants, proving that a new process without new laws and within the existing legal frameworks is possible, to the benefit of both applicants and NCAs.
The VHP offers significantly advantages for small and intermediate size companies and non-commercial sponsors, as offering adaptations on a case by case basis to meet applicants' needs before and during the procedure by simple agreements of the NCAs.
A disadvantage at the moment is that 2/27 Member States are not participating in the Voluntary Harmonisation Procedure, due to legal or procedural constraints. This issue might be positively addressed and solved by HMA action.

Option 2, can be seen as a successor of the VHP, offering by and large the same features in a new legal framework. The introduction and later modifications of a DCP/MRP would consume considerable times and costs but would ensure that all concerned MS would actively involved in the approval process of a CT. If the option is followed, it is suggested that a minimum of participating Member States should be fixed (e.g. 4 MS) to balance costs and benefits.

Option 3 is a centralised procedure requiring a regulation and giving an authorisation for the whole Community after an assessment by the EMEA. This process could also be optional and either be applicable for all clinical trials in the EU or only to certain CTs, for example for products for which a marketing authorisation issued by the Community is obligatory.

- A regulation, even if offered only as an optional procedure for the authorisation of CT, requires the maximum effort in terms of legal and procedural changes for limited numbers of CTs. About 75% of the 4000-5000 clinical trials per year are performed in one MS only. Merely 10% involve more than 4 Member States. The increased efforts to receive the authorisation in these multi-national CT could be effectively organised via the VHP or a DCP/MRP.
- The option to include all 4000-5000 CT in a centralised procedure in Europe is not realistic and would be an extreme waste of resources. The restriction to certain products for which a marketing authorisation issued by the Community is obligatory is not really comprehensible. Why should advantages of a centralised procedure only be restricted to products which require a centrally authorised marketing authorisation?

- The fees for an approval of a CT for the whole of Europe, even if not needed, are assumed to be higher than the costs in the concerned Member States only.
- An optional centralised procedure requires infrastructure and personnel at the EMEA level as well as at the NCA level, therefore multiplying costs.
- All the problems with the harmonisation of procedures between NCA and EC are not solved by any of the 3 options.

The Voluntary Harmonisation Procedure is the most effective procedure for multistate CTs at the moment and should be supported by the EU-Commission for example by money for staff and infrastructure.
An Option 4 is to be added: the national option is to be maintained for the 75% CTs which are performed in only one Member States.

The next chapter addresses possible changes of the authorisation procedures by Ethics Committees

Option 1 proposes a one-stop shop for the submission of the request for authorisations

Option 2 proposes a strengthening of networks of national Ethics Committees involved in multinational clinical trials

Option 3 proposes a clarification of the respective scopes of assessment of NCA and Ethics Committees

1.7. Consultation item n°5

requires answers to the following questions: 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?

Option 1 is generally endorsed, but also foreseen with many practical problems, as the documentation sent to the Ethics Committees contain a great part of country specific information as documentation on trial sites, on investigators including qualification documentation, on patient information and informed consent in the national languages and on insurances.
Ethics Committees are differently organised in Europe and have different abilities to work fully or partially electronically. Ethics Committees also have often lay members with no or limited access to European institutions or funding of the required IT-structure.
Options 2 and 3 are fully endorsed. Options 2 and3 could be achieved by the updating the respective guidance documents of Directive 2001/20/EC.

1.8. KEY ISSUE N°2 addresses: INCONSISTENT IMPLEMENTATION OF THE CLINICAL TRIALS DIRECTIVE

The consultation paper states that Clinical Trials Directive aims at an exhaustive harmonisation of the regulatory framework for clinical trials. Examples that this harmonisation was only partially successful and this was due to inconsistent application of the Directive by the Member States are:

- Substantial amendments
- SUSARs
- Non-interventional trials

1.9. Consultation item n°6:

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

Point 1 substantial amendments:

The paper assumes, based on the ICREL report, that different Member States define SA differently, therefore leading to more than 21000 SA per year, a more than 3 fold increase compared to 2003.
NCA might differentiate in their assessment of whether an amendment is substantial or not for various reasons. Sometimes it is a NCA task to assess parts of the documentation, which is an Ethics Committees task in another country. Some countries introduced higher requirements in compliance with Article 3 of Directive 2001/20/EC.

- The figure 21000 itself proves neither an increase nor a decrease. In 2003, which is the basis of the calculation, no definition for a substantial amendment existed in the majority of the Member States. Furthermore in 2003, in many of the Member States substantial amendments were neither reported to nor authorised by NCA. Therefore any introduction of rules for SA must have resulted in an increase.
- The figure 21000 has to be correlated with number of clinical trials in Europe. At the moment more than 22000 CT are in the EudraCT Database. Even if many of these CT are already completed, an average number of 2-4 SA per CT can be assumed, according to the current NCAs' experience.
- One should not forget that SAs are submitted by sponsors and not by NCA, following initial trial authorisation, and therefore result from changes to the protocol or related trial documents initiated by the sponsors. It is the sponsor's responsibility to differentiate between substantial and non-substantial and resultantly to decide what to submit. Therefore any increase in SA can be seen as primarily originated by sponsors.
- Circulating examples, as planned in updated guidance, of what is/what is not a SA will help to avoid over reporting
- It is perceived at the NCA level that some amendments reflect poor or incomplete planning by sponsors, i.e. necessitating changes if and when recruitment does not follow projected speed

Point 2 SUSARs:
The introduction of a Community Database for SUSARs for CT and electronically reporting is endorsed. Whenever a fully functional version of this Community Database for SUSARs for CT complies with the basis requirements of the MS to ensure the protection of the participants of Clinical trials, the national systems might be changed or abolished.
Both the national and the Community Database for SUSARs suffer from the massive over reporting by the sponsors of clinical trials. This problem to report everything, just "to be on the safe side" will not be changed by any national or community administrative measure. An update and further clarification of the Guideline to the Directive 2001/20/EC *Detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use* might reduce the numbers.

Point 3 non-interventionnel studies (NIS)

The existing definition of the Directive 2001/20/EC of non-interventional studies is considered as appropriate. As long as no generally accepted risk criteria exist, a case by case decision is necessary. An agreed list of interventions of minimal risk as e.g. mere blood sampling, certain diagnostic measures, etc might help to harmonise potential differences between MS.

The consultation paper names the following weaknesses of the inconsistent implementation of the clinical trials directive:

- Insufficient patient protection: For example, an incoherent regime of transmitting and processing information on SUSARs

- Increase of administrative costs by 90% especially by academic sponsors:

1.10. Consultation item n°7 asks:

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

For the first point SUSARs see Point 2 on page 7

For the point costs, most of the points from the numbers of substantial amendments from page 7 would have to be repeated (basis 2003, no/minimal requirements for the approval/amendments of CT). In 2003 in many of the Member States clinical trial were neither assessed nor authorised by NCA. SUSARs were not or partially reported/assessed and application of the GCP principles might not be understood as mandatory. Therefore any introduction of rules for the authorisation of clinical trials, for safety assessment and application of GCP standards must have resulted in an increase of cost. This is especially true for academic sponsors were the quality of the application dossier had to be improved mostly. The very limited database of the ICREL report, especially of academic sponsors, might also led to an over estimation of the increase of cost. Academic sponsors may in the past have been involved in trials examining authorised medicinal products, which may have been beyond the scope of the clinical trial legislation in place prior to the CTD. The requirement to demonstrate compliance with GCP in accordance with the CTD should not necessarily have increased their costs, as these guidelines should have been adhered to prior to the implementation of the CTD. Details regarding these and other costs increases would be welcome.)

The consultation paper names the following options to address the weaknesses of the inconsistent implementation of the clinical trials directive:

- Reviewing of Directive 2001/20/EC and clarifying in the points SUSAR reporting, Annual Safety Reports, substantial amendment

- Introducing a regulation to harmonise the whole CT authorisation procedure

1.11. 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?

Point 1/2: As mentioned before, a review of the guidelines to Directive 2001/20/EC, or if needed the directive itself, might improve the situation by simplifying on points like SUSARs and substantial amendments. These clarifications could be implemented in parallel to the VHP or a DCP/MRP and do not require a regulation. Since many of the problems (i.e. incorrect reporting or submissions) are not within the remits of the NCA, even a regulation will be no solution and leading to complete harmonisation. As CT are often widely heterogeneous, regulations or guidelines could hardly be exhaustive, many questions will also in the future be left open to interpretations and will require a case by case decision. The most effective way to achieve this would be consensus building via VHP/DCP/MRP or Clinical Trials Facilitation Group discussion and publishing of the results for example in Q&A documents.

1.12. KEY ISSUE N°3 ADDRESSES: REGULATORY FRAMEWORK NOT ALWAYS ADAPTED TO THE PRACTICAL REQUIREMENTS

The paper states that the Clinical Trials Directive and its implementing guidelines, has brought in regulatory obligations and restrictions which, in some cases, are widely considered as not matching practical considerations and requirements. The example given is that

- Requirements not always risk-commensurate

1.13. Consultation item n°9:

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

The Clinical Trials Facilitation Group considers the present system as flexible enough to address different risks. The CTFG is working with the EMEA inspectors working group on a risk based approach to bring facilitation as much as possible Even if accepted risk categories would exist, the reductions in requirements for any medicinal product would have to be assessed in the light whether the concrete treatment with the product fits to the reduced risk category. For example even approved medicinal products with a lot of experience and known effects in one indication can not a priori be considered of low risk in other indications.
In the case of non-commercial or academic sponsors the aim of the CT might be the optimising a therapy with products holding marketing authorisations, but it might also be a First in Human application of cell based product or a gene therapy. Therefore also risk minimisation according to the sponsor status is considered impossible.
Also the minimisation of requirements as monitoring or other general GCP-requirements according to the sponsor status can be inappropriate as for example the results of therapy optimising studies often serve as the basis of therapy recommendations and have therefore to be of the highest quality to ensure the optimal treatments of patients afterwards.

In the review of current guidance documents a categorisation of the documents under the aspects of risks should be implemented wherever possible. The existing possibilities to reduce the documentation according to risk e.g. the simplified IMPD, adapted monitoring, labelling according to the marketed product etc. should be highlighted in the any revision of guidelines.

The next point of the Consultation document states that the requirements are not always adapted to the practical circumstances

The example given is that the Clinical Trials Directive is based on the concept of one single sponsor per (multi-national) clinical trial. It is reported to be difficult for sponsors, in particular “academic”/”non-commercial” sponsors, to take responsibilities for clinical trials performed in another Member State.

1.14. Consultation item n°10:

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

The concept of one sponsor per trial is considered as important by the CTFG to ensure that the NCA and the Ethics Committees have one addressee to enforce for example patient protection. Also a high quality of data might be easier to achieve, if the responsibility is in one hand, rather than in the hands of many sponsors per trial. Many examples exist, where “academic”/”non-commercial” sponsors used successfully existing international organisations of researchers to serve as sponsor for multi-national CTs. Nevertheless in at least two Member States (UK and Spain) the concept of a single sponsorship is questioned, although for differ-

ent reasons. A facilitation in the case of “academic”/”non-commercial” sponsors might be worthwhile considering, although legal aspects of responsibility are to be clarified then.
Many practical problems with clinical trials with several sponsors are foreseen in the case of VHP, DCP/MRP and especially in a centralised procedures.

The consultation paper names the following weaknesses of a regulatory framework not always adapted to the practical requirement are described as follows:

- Increased costs
- Creation of disincentives to conduct clinical research in the EU, in particular for “academic”/“non-commercial” sponsors
- The long-term consequence is that patients are deprived of innovative treatments and the competitiveness of European clinical research is reduced.

The consultation paper refers to the many guidance documents that were developed in relation to Directive 2001/20/EC and that would have to be adapted (Safety/SUSAR reporting; labelling; content of application, insurances)

1.15. Consultation item n°11 asks:

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?

The Clinical Trials Facilitation Group supports a revision of the respective guidelines in the context of the existing legal framework whenever possible.

The consultation paper asks for the need of a review of the existing Directive and adaptation of the requirements to practical necessities

Examples for issues are asked, which are grounded in the legislation itself, i.e. areas where changes to implementing guidelines would not have effect.

1.16. Consultation item n°12 asks:

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?

In many (but not all) Member States regulations for clinical trials in emergency situations have been implemented, although informed consent in these emergency situations is problematic. This led to the situation, that in some Member States these CT can not be performed. Directive 2001/20/EC should be adapted accordingly to enable these studies.

Procedures as the Voluntary Harmonisation Procedure or DCP/MRP could be introduced into the directive.

The consultation paper asks for a r*eview of the existing Directive and excluding clinical trials of “academic” sponsors from the scope of the Directive*
The paper states that:
this option would mean an outright exclusion of so-called “academic” sponsors from the rules of the Clinical Trials Directive. This would mean that national rules set by Member States would apply. This would also mean that, in accordance with the Community legislation set

out above, results of these clinical trials cannot be referred to in the framework of a an application for a marketing authorisation in the EU.

1.17. Consultation item n°13 asks:

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

The CTFG would strongly disagree for the following reasons:

- A commonly accepted definition of an "academic" sponsor does not exist and was not achievable even after intensive discussions in many fora. This precludes any changes to the directive in this respect.
- Two standards of protection for the participants of clinical trials and for the data (GCP standards) would not be acceptable. In the case of non-commercial or academic sponsors the aim of the CT might be the optimising a therapy with products holding marketing authorisations, but it might also be a First in Human application of cell based product or a gene therapy. A differentiation between commercial/ non-commercial sponsors is inappropriate to ensure the protection of the participants and data reliability.
- What should be a legal basis to deprive commercial sponsors with "low risk" studies of facilitations and to grant facilitations to non-commercial sponsors for "high risk" CT?
- Giving the right to regulate back to the 27 Member States might result in a situation before the introduction of Directive 2001/20/EC with different requirements/increased complexity and might create even a reduction of numbers of multinational CT of "academic" sponsors. (e.g. multi-national CT by EORTC)
- The possibility of abuse by commercial sponsor using "academic" sponsors as a dummy can not be excluded.

1.18. KEY ISSUE N°4 TO BE ADDRESSED: ADAPTATION TO PECULIARITIES IN TRIAL PARTICIPANTS AND TRIAL DESIGN

The consultation paper states that clinical trials are performed in many different settings, and with different groups of trial participants. This raises the question whether the various constellations are adequately addressed. Examples are:

- clinical trials in the paediatric population

- clinical trials in emergency situations

1.19. Consultation item n°14 and n 15ask:

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?

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?

The CTFG supports an update of Directive 2001/20/ECin order to enable/facilitate this research in all Member States while ensuring the safety and the rights of especially vulnerable populations. The regulations and the experience of the Member States, which already have regulations in place, could be used as a basis of the changes.

1.20. KEY ISSUE N°5 ADDRESSES: ENSURING COMPLIANCE WITH GOOD CLINICAL PRACTICES ("GCP") IN CLINICAL TRIALS PERFORMED IN THIRD COUNTRIES

In this chapter some reasons for EU-based industry to conduct clinical research outside the EU are given. The commission paper highlights that any disregard of the rules that protect clinical trial participants is inacceptable and calls for determined action – independently of where the clinical trial has been performed. It is further expressed that it is unacceptable and calls for determined action by the regulator, if clinical trials performed in these third countries exploit the particular vulnerability of their population.

1.21. Consultation item n°16 asks:

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

The view of the Commission is strongly supported. The CTFG has no further comments

In the next chapter the following issues are addressed:

- Weaknesses with the following option to address
- Supporting regulatory framework and capacity-building where necessary
- Self-regulation by EU-based sponsors
- Strengthening international cooperation in GCP inspection and mutual recognition of GCP rules
- Optional assessment of 3rd-country clinical trials by the EMEA
- Strengthening a culture of transparency
- Strengthening scrutiny of clinical trials results of which are submitted to the EU, or which are financed in the EU

1.22. Consultation item n°17 asks:

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

In addition to the option *Optional assessment of 3rd-country clinical trials by the EMEA also* experienced Member States should be considered as a partner of organisations like the WHO for the assessment of 3rd country CT.

The last point *Strengthening scrutiny of clinical trials results of which are submitted to the EU* and especially the points

- 1st "linkage": The results – be they negative or positive – of a clinical trial performed in a third country are submitted in the process of an application for a marketing authorisation for a medicinal product in the EU
- 2nd "linkage": The results of a clinical trial performed in third countries, are submitted in the dossier of a request for authorisation of a clinical trial in the Community

are considered as important requirements to enable the high quality assessment by the Member States in order to ensure the safety of participants of clinical trials.

1.23. Consultation item n°18 asks:

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?

The Clinical Trials Facilitation Group has no further points to address and considers SME aspects as sufficiently covered