International Public Affairs
Boulevard de la Plaine, 17
B-1050 Brussels, Belgium

EU Representation Office
Tel. +322 554 6212 – Fax. +322 554 6174

Register of interest representatives #:
4263301811-33

Worldwide BioPharmaceutical Businesses
Public Affairs

Response to the public consultation on the concept paper 'Revision of the "Clinical Trials Directive" 2001/20/EC'

SECTION 1: COOPERATION IN ASSESSING AND FOLLOWING UP APPLICATIONS FOR CLINICAL TRIALS

Consultation item no. 1: Do you agree with this appraisal? Please comment.

[Yes.] We agree with the assessment that individual national submission and review procedures have the following consequences:

- largely identical information has to be sent to several different Member States, which creates unnecessary administration
- the requirements set out in the Clinical Trials Directive are applied differently in the different Member States leading to divergent points of view on the same application

The proposal for submission of CTAs through a single EU portal would remove some of the administrative burden of submitting largely identical information to the individual MS providing that it is clear that there needs to be a single package of information for all Member States; additional national requirements should not be permitted.
However, it would not address one of the major issues negatively affecting our later stage trials (Phase IIb trials onwards), that of multiple and divergent assessments of clinical trials.

Consultation item no. 2: Do you agree with this appraisal? Please comment.

[Yes.] We agree with the Commission that continuing to have assessments of CTAs conducted independently in each Member State would not address the issues we face with conducting later-stage trials. Too often, a rapid initiation of the trial is hindered because of significant variations in assessments leading to divergent requests for

additional information. In addition, variance across member states in the times taken for assessment of the same CTA dossier also causes major hurdles for the rapid initiation of trials.

Consultation item no. 3: Do you agree with this appraisal? Please comment.

[No.] Although we agree with the Commission that the proposal for a central assessment of CTAs for all clinical trials by a Committee representing all Member States would make this approach unworkable, costly and ultimately unattractive, we continue to believe that the following, slightly adapted approach, would be more attractive and could be workable:

At the option of the applicant, for multinational clinical trials, a centralised reviewing team representing the Member States where the applicant proposes to conduct the clinical trial and other experts, as appropriate, from across the EU could be convened to assess and provide an opinion on the CTA. The opinion of this reviewing committee should be on behalf of the whole EU. Approval of the CTA following this single assessment should allow the trial to be conducted anywhere within the EU (subject to positive opinions from relevant ethics committees).

Such an optional centralised procedure offers many advantages:
(1) it avoids the current duplication of CTA assessments and the well over one hundred 'country specific requirements' that do not add to patients' protection and the quality of a trial;
(2) resources within the NCAs will be released as there would not be multiple assessments of the same data;
(3) it provides access to the widest pool of (regulator) expertise across the EU, which is particularly important for advanced therapies, rare diseases, and/or innovative or complex study designs (e.g., complex adaptive design).

The ethical standards that form part of GCP and the "Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine" could form the basis for the assessment of ethical aspects of clinical trials. The long-term objective should be a completely EU-managed ethics system. In the meantime, the assessment roles of ethics committees and NCAs must be clarified as soon as possible.

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

[Yes.] Overall we feel that the catalogue, as laid out by the Commission is complete. However, we feel that there should be a greater emphasis on the aspects under a) on the assurance of safety of subjects participating in the trial.

Consultation item no. 5: Do you agree to include the aspects under a), and only those aspects, in the scope of the CAP?

We would rather see a procedure, as described in our response to Consultation Item No. 3, which results in a centralized review from the concerned member states and a single decision on a CTA within defined timelines that is applicable across the entire EU.

The reason for this view is that while we agree that the role of the national competent authorities should concern the risk/benefit assessment, as well as aspects related to quality of the medicines, we do not believe that the 'coordinated assessment procedure' as proposed by the Commission is the most appropriate approach. We are concerned that a CAP would not result in a harmonized view being taken on a CTA, and would thus lead to delays in approval of the trial. The proposed CAP still leaves a single decision on CTA authorization per Member State, allowing differing decisions to be taken and different timelines for making that decision. The uncertainty of differing decisions and timings per Member State will continue to affect the competitiveness of the EU as a place for clinical research.

Furthermore, we support that the role of national competent authorities and ethics committees should be better defined. However, Pfizer does not necessarily agree with the statement in the Concept Paper that "ethical issues clearly fall within the ambit of Member States and should remain there". We would question what ethical issues that are being assessed by national ethics committees are based on purely national legislation. Pfizer therefore supports the long-term aim of an EU-managed ethics system. However, we recognise the environment is not yet ready to support such an approach. One of the outputs from this consultation should be to initiate the identification of, and to set in motion, the changes needed to overcome the barriers to achieving an EU approach to ethics. This would need to be pursued independently of changes to the clinical trials legislation.

As a first step, Pfizer recommends at least a high level dialogue between the lead members of the national ethics committees, which would facilitate the formation of a European perspective on major issues.

Consultation item no. 6: Which of these approaches in preferable? Please give your reasons.

[Approach 2.] We believe that divergent assessments of clinical trials are a major issue negatively affecting the conduct of later stage trials. Thus a key outcome from a coordinated approach to assessing CTAs should be to reach a consistent and standardized result. This needs to be achieved through the most efficient approach, which in our view is option 2.

Although Option 3 ensures an EU-wide decision to be taken on CTAs, we fear that this option would be time-consuming and could lead to further delays; as already identified having an EU-wide committee could be resource-intensive. Pfizer could support this option as the best alternative to option 2, if measures are taken to ensure that this approach does not lead to unnecessary delays. Clear timelines should, for example, be set for the decision-making process.

Adopting Option 1 would permit Member States to take a unilateral decision on a CTA which could easily result in a non-standardized outcome of assessments of CTAs. Furthermore, we have difficulty understanding how a single Member State could justify how a 'serious risk to public health or safety of the participant' applies only in that country; any serious risk to public health or safety of the participant should be applicable across all Member States. Pfizer therefore believes that this option would undermine the objective of a co-ordinated review process.

Consultation item no. 7: Which of these approaches in preferable? Please give your reasons.

[Approach 3.] We prefer option 3, 'Coordinated assessment procedure completely optional'. Our least favoured is option 1, 'Coordinated assessment procedure mandatory for all clinical trials'.

Use of a coordinated approach to CTA assessments should be completely at the option of the sponsor of the trial. There are many factors to be considered when designing and running a clinical trial. A 'one-size-fits-all' approach is not appropriate.

We appreciate that there may be costs in setting up the Community Assessment Procedure and that the recovery of those costs may not be guaranteed without the CAP being mandatory for at least some trials. However, we believe that such an investment is needed to help ensure that the competitiveness of the EU as a place to conduct clinical research is enhanced. Thus, optionality in the choice of route for CTA approval is an imperative.

Consultation item no. 8: Do you think such a pre-assessment is workable in practice? Please comment.

Pfizer supports the concept of identifying those trials where the risk to trial subjects is low and adapting the assessment process as necessary. However, we do have concerns that a pre-assessment of the 'type' of trial could add to the bureaucracy, workload and timelines for obtaining CTA approval in the EU. We could be supportive of a pre-assessment procedure to identify these 'low-risk' trials if such a process follows the following principles:

- Pre-assessment is entirely optional at the sole request of the trial sponsor
- The pre-assessment is to be performed at an early stage of trial design;
- The process for pre-assessment is rapid and requires limited documentation for the assessment;
- Only one Member State makes the assessment that is then recognized, without question by all other Member States.

In addition, it will be important that the criteria for determining whether a trial is "low risk" are clear, in order to avoid divergent national interpretations. In this respect, Pfizer notes that while the criterion set out in sub-paragraph (a) appears to be straightforward, the criterion set out in sub-paragraph (b) is somewhat vague and open to interpretation in practical situations.

It is unclear to Pfizer why an authorization per Member State would still be required under the proposed CAP. We envisage an EU procedure to involve a single assessment of the CTA on behalf of the whole EU. Approval of the CTA following this single assessment should allow the trial to be conducted anywhere within the EU (subject to positive opinions from relevant ethics committees), without the need for a further authorization from the Member States concerned.

However, if an obligatory single authorization per Member State prior to the commencement of a clinical trial is imposed by law, as proposed by the European

Commission, then the law should also be clear as to what the legal consequences are if such authorization is not forthcoming. In this respect, the 'tacit approval' system has been helpful, in that it imposes a clear deadline with legal consequences if no action is taken by the Member State in question.

SECTION 2: BETTER ADAPTATION TO PRACTICAL REQUIREMENTS AND A MORE HARMONISED, RISK-ADAPTED APPROACH TO THE PROCEDURAL ASPECTS OF CLINICAL TRIALS

Consultation item no. 9: Do you agree with this appraisal? Please comment

[Yes.] Pfizer welcomes a more harmonised approval system with defined, proportionate requirements. However, this should not mean that the requirements should be the same for all trials; the competitiveness of Europe as a place to conduct clinical research can be improved through maintaining flexibility and providing options for sponsors to have different review processes/timetables and requirements depending on the type or circumstances of the clinical trial.

Furthermore, such requirements should not expand the scope of the Clinical Trials Directive: it should be made explicit that non-interventional trials are not covered by the revised clinical trials legislation. We suggest that the European Commission develop a separate legal regime for non-interventional trials.

Consultation item no. 10: Do you agree with this appraisal? Please comment.

[Yes.] We maintain our belief that the nature/stringency of the requirements and obligations should not be driven by the status/identity of the sponsor. However, we do recognise that some sponsors find difficulty in complying with the legislative requirements. We also recognise that this can have an impact on the ability for those sponsors to conduct clinical research in the EU.

We believe that those provisions of the legislation that cause difficulty for 'academic' sponsors should be identified and reviewed. The impact of these provisions on the safety of trial participants should be considered. If, by excluding these provisions, there is no impact on the safety of clinical trial participants, the reasons for including those provisions in the clinical trial legislation and applying them to all sponsors need to be re-considered.

This approach would then remove those elements of the legislation that are problematic for 'academic'/non-commercial sponsors while maintaining the high standards of patient safety and ensuring consistency in application of the EU legislation across all clinical trials' sponsors.

Consultation item no. 11: Do you agree with this appraisal? Please comment.

[Yes.] Pfizer strongly supports the adoption of a risk-adapted approach to the rules for the content of the application and for safety reporting. However, we are concerned that a single solution to a risk-adapted approach will not be implemented easily.

We believe that there needs to be a greater awareness, discussion and understanding of what constitutes a risk-based approach to the governance of clinical trials. There needs to be an understanding, acceptance and encouragement from NCAs for risk-based approaches to managing clinical trials. Risk-based approaches must be justifiable with decisions based on scientific grounds.

Pfizer notes that the European Commission suggests to base the requirements on the detailed guidance documents CT-1, CT-2 and CT-3. It should be carefully considered whether the principles set out in these documents are suitable for inclusion in the annex.

With regard to the safety reporting requirements we believe the EU legislation should be amended to ensure that quality rather than quantity is the main objective, i.e. the information obtained from safety reporting in clinical trials is useful and meaningful. It needs to be comprehensive enough such that, following analysis, a thorough understanding of the safety profile of the products and procedures used in the trial is available. Ensuring such changes to the SUSAR reporting paradigm could result in having more meaningful (medically relevant) safety reports that ultimately aid subject safety in the trial and patient safety on the market. We recognise, however, that agreement on how to change the system to achieve this will take time.

With regards to divergent interpretation on data requirements, these relate particularly to inconsistency in the documentation required by the different NCAs in order to assess CTAs. These mostly relate to the Quality data package, both in terms of the documentation format and sometimes the substantive data content, supplied in relation to investigational medicinal products (IMPs) used in the study (test drug, comparator(s) and placebo).

However, rather than there being very many differences in the actual documents required between the Member States for the CTA, the more serious concern is the individual NCA expectations on the actual data content for some of the EU common documents, e.g., differences in the NCA interpretations of how certain question in the EU Annex 1 should be answered, and differences in the interpretation of some of the Directive's definitions (e.g., Sponsor, Applicant, Legal Representative etc).

Some Member States also demand that the updated documents being supplied in a substantial amendment package must have not only a summary of changes (standard practice), but also a "track changes" version as well as a clean version and, in some cases, an actual justification for each of the changes (French requirement).

The NCAs also have different levels of translation requirements, e.g., some will accept a CTA fully in English, whilst others will demand various documents be translated for submission.

All these differences add to the administrative complexity and burden of conducting multi-country clinical trials in the EU, and would not seem to be essential to the protection of patients, public health or data quality.

Consultation item no. 12: Are there other <u>key aspects</u> on which more detailed rules are needed?

Any new/revised legal instrument should set out a range of detailed procedures and provide clearer definitions (e.g. IMP, legal representative, reporting procedures). It should also provide for simplified procedures (e.g. for authorization of a clinical trial) or more flexible requirements (e.g. concerning the Annual Report) which could apply to low-risk clinical trials.

Consultation item no. 13: Do you agree with this appraisal? Please comment.

Pfizer agrees with the proposal for a narrowed definition of investigational medicinal product. We also agree with the appraisal concerning the uncertainties of classification of non-investigational medicinal products (nIMPs) and the need for establishing clarity for their proportionate requirements.

We support the creation of the term 'auxiliary medicinal product', and its definition, if the term 'auxiliary medicinal product' replaces the term 'non-investigational medicinal products'. We do not support the adoption of a third definition. It will also be essential that there is a high degree of clarity regarding which products fall within the definition of 'auxiliary medicinal product'.

The acceptability of this proposal is reliant on ensuring that the requirements for 'auxiliary medicinal products' are reasonable, practical and proportionate in relation to the risks of their use in the trial. Also critical for this proposal's acceptability is a consistent application of the requirements across all Member States.

Pfizer further proposes that consideration should be given to the development of an approach that would permit approval for a particular auxiliary medicinal product to be used across a number of trials. This could be particularly useful where such a product is being used as a challenge agent in a series of trials. The use of and data required for a particular challenge agent could be discussed and agreed in a single procedure ahead of the submission of any CTAs/ protocols for the trials.

Consultation item no. 14: Which policy option is favourable in view of legal and practical obstacles? What other options could be considered?

Pfizer does not consider the suggested options to be appropriate. Insurance requirements should be maintained for all trials. The cost relating to such insurance for trials conducted in the EU is generally not excessive. This should particularly be the case for low-risk trials, where insurance costs can be lower than for high-risk trials. Requiring insurance for all trials provides legal certainty and clarity to all stakeholders in case of injury or death. Making Member States responsible for providing insurance will likely lead to higher costs.

Consultation item no. 15: Do you agree with this appraisal? Please comment.

[Yes.] Pfizer has not experienced major issues or concerns with the requirements of a sponsor and whether there is a need for a single sponsor.

Consultation item no. 16: Do you agree with this appraisal? Please comment.

Pfizer supports a full harmonization across Member States of the rules applicable to emergency clinical trials. In our view, the best way to achieve such harmonisation is through adoption of the EU clinical trials legislation in the form of a Regulation.

SECTION 3: ENSURING COMPLIANCE WITH GOOD CLINICAL PRACTICES IN CLINICAL TRIALS PERFORMED IN THIRD COUNTRIES

Consultation item no. 17: Do you agree with this appraisal? Please comment.

[Yes.] Pfizer supports further international cooperation in the regulation of clinical trials, encourages further dialogue with all stakeholders on GCP compliance and supports capacity building in relevant third countries. However, Pfizer considers that any additional regulatory requirements should be reviewed carefully to avoid further impediments to innovation. Pfizer has rigorous procedures and assurance processes in place to ensure that clinical trials are conducted in accordance with recognized international ethical standards, irrespective of whether they take place in developed or developing countries.

In principle, Pfizer does not object against including point 2.7.2.4 of the detailed guidance CT-1 in the risk-adapted rules to be included in the annexes to the new clinical trials legislation. However, the impact of a codification of point 2.7.2.4 will be limited, because it must already be complied with. Similarly, Pfizer does not object if study results will only be accepted in the context of an EU marketing authorization process if the trial had been registered in the EU clinical trials database EudraCT. If imposed on all stakeholders, this requirement could well contribute to a better understanding of the importance and quality of clinical trials conducted in third countries.