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Worldwide BioPharmaceutical Businesses
Public Affairs

Assessment of the Functioning of the 'Clinical Trials Directive' 2001/20/EC

Public Consultation Paper
European Commission ENTR/F/2/SF D(2009) 32674, 9 October 2009

Comments from Pfizer

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

The implementation of Clinical Trials Directive 2001/20/EC ("the Directive") across the EU has resulted in a number of benefits to protect subjects participating in clinical trials. The overall benefit to subject protection was seen through a significant standardisation of clinical trial practices across Europe.

Specific examples exist that help to demonstrate where the benefits of the Directive have resulted in improved patient protection. These include:

- A documented requirement to report all SUSARs to National Competent Authorities (NCAs) and ethics committees in the same timeframe across the EEA, resulting in the same information being submitted. Patient protection is enhanced by assurance that safety data from trials is being collected, analysed and acted upon in a co-ordinated manner.
- Pan-European alignment of standards and approach for assessing the quality, safety and efficacy of products used in clinical trials. This ensures that data submitted to support the conduct of trials in the EU is of a consistent high quality and is being assessed against high standards by all Member States. An example from Pfizer where this has helped improve patient protection is a multi-country paediatric study which was submitted to the French NCA for initial authorization. During the evaluation of the protocol, AFSSAPS required the creation of an independent safety monitoring committee before they would approve the conduct of the study. As a result of which, the Pfizer international team set up this committee in all participating countries. This requirement improved the patient protection in all countries. Prior to the implementation of the Directive, France had a system where a 'Notice of Intent' was submitted and the data did not undergo a detailed review.
- The standardisation of ethics committees processes brings a major improvement in terms of consistency of ethic committees opinion. Before the implementation of the Directive, the ethics committees had non-unified approaches often with inconsistent opinions/views.
- Greater consistency in expectations from GCP inspectors. Although detailed GCP guidelines were available before implementation of the Directive, there was great scope for variable interpretation. As a result different stakeholders approached some aspects in a different manner. The Directive has provided an opportunity for a more consistent approach by GCP inspectors across the EU. Having a greater understanding and consistency from GCP inspectors means that GCP can be applied to the greatest benefit for study participants.

In spite of these clear benefits to patient protection, Pfizer welcomes the Commission's initiative to assess the functioning of the Directive. Pfizer believes that there remain areas for improvement. We outline those key areas throughout our response to this public consultation. We hope that as a result of this public consultation,

these areas for improvement will be addressed. This should then help reduce the bureaucratic burden of the EU legislation with no detrimental impact on patient protection.

KEY ISSUE N°1: Multiple and divergent assessments of clinical trials

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

The Commission has captured the key aspects of the issue in its consultation paper. The multiple and divergent assessments of clinical trials is a major issue negatively affecting our later stage trials. We often try to conduct multinational clinical trials, using the same protocol, in multiple Member States. Too often, a rapid initiation of the trial is hindered because of divergent requests for additional information and significant variations in assessments of the same CTA dossier.

We would like to see an optional EU procedure introduced such that there are not multiple assessments of the same data for the same trial. We envisage such an EU procedure to involve a single assessment of the clinical trial application 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 (pending positive opinion from relevant ethics committees).

Other practices should be introduced that facilitate sharing of views from regulators across multiple Member States during the review of a CTA. This would enable a discussion of the key scientific issues. Such pan-EU discussion would be particularly impactful where there is a lack of agreement between MS on a particular CTA.

In addition, on numerous occasions there has been a divergence in the assessment between the NCA and the ethics committees for a submitted CTA. While there is sometimes a resolution of the divergence, this is not always the case. We recognise that the NCA and the ethics committees have a different focus/expertise and, as such, they may assess different aspects of the CTA. Furthermore, experience has shown that some ethics committees may not be aware of existing regulatory guidelines and/or they may have different views on the protocol design in contradiction with such guidelines. To that end, we recommend that a system be developed with the goal of achieving better cooperation between the NCAs and the ethics committees.

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

The Commission has captured the key weaknesses in its consultation paper.

We believe that the administrative burden has increased since the introduction of the provisions within the Directive. However, we are not in a position to provide data to quantify the increase in administrative burden and support this belief.

Having a ‘patchwork’ of separate assessment procedures means there is a need to make and provide responses to multiple applications pursuant to which multiple authorities are assessing the same data for the same trial. This provides for an additional level of bureaucracy and uses unnecessary resources at the sponsor level for purely administrative matters. Furthermore having a multitude of national regulators conducting the same review leads to differences in interpretation by the different Member States. At the sponsor level this results in a substantially greater complexity in managing multinational clinical trials.

The inconsistent approach by different Member States leads to many national requests for additional documentation to be included in CTAs (e.g. specific forms for national clinical trial registries, comparative tables, specific forms for collection and storage of biological samples). Responding to such requests and providing the additional information adds to the cost and bureaucracy of initiating clinical trials in Europe.

These additional costs, bureaucracy and detrimental consequences contribute an incentive for pharmaceutical companies to move their clinical research operations and conduct clinical trials outside Europe.

Consultation item n°4: Can you give indications/quantifications/examples for the impact of each option? Which option is preferable? What practical or legal aspects would need to be considered in further detail?

Pfizer believes that an efficient and competitive clinical trials framework in Europe will need to rely on a combination of both voluntary co-operation of NCAs and an EU-wide approach to streamlining the NCA authorisation process.

For large clinical trials to be conducted in many Member States, an optional EU procedure is preferable. Within this EU procedure there should be a single CTA. The regulatory assessment of this CTA should be performed by one regulatory authority. This EU approach needs to be optional, at the request of the sponsor; as in some situations there may be valid reasons why an EU approach to the assessment of a CTA for a clinical trial to be conducted in several Member States would not be preferred. We recognise that the introduction of an EU approach will require a significant change to the current EU legislation.

An EU procedure offers many advantages for multinational clinical trials for any sponsor, be this academic, industry or non-governmental organisations such as:

- It allows for the preparation and submission of a unique, standardised CTA dossier and avoids the current duplication of CTA assessments. The well over one hundred (official and unofficial), 'country specific requirements' that do not add to patients' protection and the quality of a trial would disappear.
- Resources within the NCAs will be released as there would not be multiple assessments of the same data.
- It provides access to the widest pool of expertise (regulator) across the EU which is particularly important for advanced therapies, rare diseases, and/or innovative or complex study designs (e.g. complex adaptive design)

Since many clinical trials conducted in the EU may only be conducted in one or a small number of Member States (particularly for early phase trials), using the EU-wide approach may be unnecessary. Therefore, Pfizer believes that the existing national approach should still be retained.

An EU procedure will take many years to agree and implement. In the meantime, there remains an urgent need to optimise the procedures under the current legislation. Thus Pfizer advocates that the Member States should co-operate to ensure efficiency of these processes. The output from this public consultation should continue to strongly encourage and support this co-operation.

Pfizer welcomes a more harmonised approval system. Whatever the future process will be, the competitiveness of Europe as a place to conduct clinical research can be maintained or improved through maintaining flexibility and providing options for sponsors to have different review processes/timetables depending on the type or circumstances of the clinical trial.

Consultation item n°5: Can you give indications/quantifications/examples for the impact of each option? Which option is preferable? What practical or legal aspects would need to be considered in further detail?

Pfizer does not necessarily agree with the statement in the Public Consultation that "ethical issues clearly fall within the ambit of Member States and should remain there". We find it difficult to recognise what ethical issues that are being assessed by national ethics committees are based on purely national legislation. We believe that the key ethical standards by which trials should be assessed are GCP (an ICH/CHMP standard) and the Council for Europe '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' (http://conventions.coe.int/Treaty/EN/Treaties/html/164.htm)

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 public consultation should be to initiate the identification of, and to set in motion, the changes needed to overcome the barriers to achieving an EU ethics approach. This would need to be pursued independently of changes to the legislation.

However, as a first step Pfizer recommends at least a high level dialogue between the lead members of each national ethics committees, which would allow for forming a European perspective on major issues.

Pfizer also strongly agrees that the scope of assessment between the NCAs and the ethics committees needs to be given greater legal clarity and reinforced at a European level. Clear delineation of the respective NCA and ethics committee assessment roles should help streamline the review process. We recognise that defining the respective roles clearly enough, so that they are consistently applied across the EU, will be difficult. Pfizer believes that, in principle, ethics committees should focus their attention primarily on study feasibility, ethical considerations and patients' rights, while competent authorities should perform the scientific/technical assessment to ensure patients' safety.

KEY ISSUE N° 2: Inconsistent implementation of the Clinical Trials Directive

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

Substantial amendments

We agree that this is a major issue for Pfizer. Our key concern is where NCAs have unilaterally developed their own guidelines and rules. Often these go beyond the determining factors laid out in the legislation and associated EU guidelines. For example France has issued national requirements with the notion of "substantial amendments for information". This results in the requirement to submit to the NCA in France certain amendments "for information" that at the EU level are considered non-substantial and therefore are not required to be submitted.

A further requirement is for greater standardisation of requirements for documentation supporting amendments, and the assessment of amendments across Member States. We propose the following:

- development of a definitive list of changes that are considered non-substantial amendments;
- implementation of a standardised system in which the sponsor can submit amendments for notification only (rather than for authorisation) to the NCA and to the ethics committees;
- greater clarity in defining the types of substantial amendments which would need only an ethics committee review or an NCA review

SUSAR Reporting

We believe there is an issue around over-reporting of SUSARs. The EU legislation should be amended to ensure that quality rather than quantity is the main objective, i.e. the information obtained from SUSAR 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) SUSAR 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.

A second issue relates to SUSARs being reported to too many locations i.e. EudraVigilance and individual NCA. Once an AE is considered a SUSAR the rules across Member States are not consistent in outlining where to report. Pfizer advocates the centralisation of reporting duties, in the same way that pharmacovigilance reporting is being centralised, through EudraVigilance. The concerns seem to be similar and there would be obvious benefits to such an approach. A centralized system would notably imply harmonized deadlines to report and would avoid multiple-reporting problems. In this regard, we would be strongly in favour of reporting all SUSARs to the EudraVigilance database only, instead of submitting the same information several times to all the various Member States. Using EudraVigilance as a unique European database recognised and accessible by all Member states would be a better use of resources and provide a valuable EU-wide knowledge-base.

There currently may not be agreement among Member States on matters such as waivers for unblinding of SUSARs. For example, a recent clinical trial protocol required an unusual unblinding waiver in order to maintain integrity of efficacy data. The waiver was accepted by each EU Member State applied to except for Spain. As a result, Spain was not included in the trial.

Pfizer also has concerns at the complexity of the current guidance on SUSAR reporting, including in particular the lack of clarity and Member State divergence in relation to the definition of investigational medicinal product (IMP) and non-IMP (NIMP). We note that the UK MHRA has found the need to prepare algorithms

to distinguish IMP from NIMP, and other NCAs take different opinions in this regard, leading to divergence in reporting requirements. This situation adds to the difficulty and administrative burden of conducting multi-country trials in the EU.

Scope of the Directive - Interventional Versus Non-Interventional Studies
Pfizer supports the Commission in pointing out that individual Member States should not subject non-interventional studies to the strict requirements of the Directive. As a clinical trial sponsor and MAH, we have several examples where a clinical trial was considered as an interventional trial in some Member States, and as a non-interventional trial in other Member States. We had a recent instance where a clinical trial involving one of our approved products was considered as non-interventional in the Netherlands, but it was considered as interventional in the other Member States. This led to different regulatory requirements depending on the country, leading to unnecessary bureaucracy. Pfizer would welcome a harmonized interpretation of the definition of an interventional trial in order to avoid this situation.

In addition to the significant issue of differing approaches to interpreting the legislative requirements, key examples of which are given above, additional examples of divergent interpretation 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). Other examples of differences in documentation requirements i.e. not specified in relevant EU guidance supporting the Directive as common requirements for the EU CTA package include:

- Chosen Gender Justification (Germany),
- GCP & GLP Declarations (France),
- Medical Care after End of Trial (Germany),
- Photosafety Testing Statement (Germany),
- Protocol Signature Page (Austria, Bulgaria, Germany, Italy, Poland).

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

Pfizer concurs with the Commission that an incoherent regime of transmitting information to NCA, ethics committees and investigators has a substantial impact on the bureaucracy of managing the safety information. This could subsequently impact the protection of patients:

- If highly important information is not disseminated in a timely and consistent manner, such information may not reach the subjects in the trial leading to diminished patient protection. Similarly such information cannot be used to assess the benefit/risk profile of the drug.
- However, if all SUSAR information is communicated, NCA, ethics committees and/or investigators may become so overwhelmed with information that they miss or underestimate important information.

Pfizer recommends that the EU legislation should be amended to ensure that quality rather than quantity is the main objective for safety reporting, i.e. the information obtained from SUSAR reporting in clinical trials is useful and meaningful.

Some Member States such as Germany and Austria have already implemented detailed requirements in terms of reporting of SUSARs to NCAs, ethics committees, and investigators. We recommend that requirements in this area be harmonised across the European Union. For example, in Germany, detailed obligations to report SUSARs both for sponsors and the respective NCA are stipulated in the GCP Ordinance[1] If the sponsor is also MAH or has applied for a marketing authorization, there is some overlap with the reporting obligations to the NCA pursuant to Sections 63b, 63c of the German Medicinal Products Act[2] as well as the reporting obligations pursuant to the Ordinance on Manufacturing of Medicinal Products and Active Ingredients[3] which - other than the GCP Ordinance - require the MAH to report also SUSARs unrelated to a clinical trial. The differentiation of reporting obligations depending on the status of the MA and the source of information as set out in the EU guidance supporting the Directive has not been adopted by the GCP Ordinance although this would, in our opinion, improve the quality of the reports and make the work of the ethics committees more efficient, as the ethics committees are overwhelmed by the amount of unclassified SUSAR reports coming, *inter alia*, from the spontaneous reporting of adverse drug reactions.

We agree that the inconsistent implementation of the clinical trials legislation has had a substantial impact on the administrative aspects of managing clinical trials. As a sponsor wishing to conduct trials in the EU (often with a rapid start-up), we have tended to need to provide more resource to ensure that the administrative aspects are quickly addressed.

Consultation item n° 8: Can you give indications/quantifications/examples of 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?

Pfizer believes that while a review of the Directive with the aim to clarify provisions would be a step in the right direction and could result in an improvement in consistency of approach, we feel that ultimately such a revision would prove to be insufficient. We remain with the belief that a revised Directive will retain room for interpretation such that the current high levels of bureaucracy arising from the differing approaches by Member States will not be addressed.

Pfizer therefore believes that in order to create sufficient legal certainty and reduce the level of different national interpretation, the best option would be for the EU clinical trials legislation to be adopted as a Regulation. This Regulation would need to provide the flexibility to permit trials that are to be conducted in only one or a few Member States to be reviewed under local procedures and late-phase multi-national trials to be reviewed a single time through an efficient centralised review system.

There is no single reason why divergent assessments of CTAs have become an issue. From our experience, divergent assessments are results of a combination of factors including:

- Member States applying their old national approaches within the EU regulatory framework. Since the legislation was adopted as a Directive and not a Regulation, Member States were permitted to take this approach. The situation was made worse by the lack of an explicit requirement that Member States co-operate when reviewing CTAs. The setting-up and functioning of the HMA Clinical Trials Facilitation Group came too late to avoid the entrenchment of individual national approaches.
- Our experience has highlighted that it is clear individuals assessing CTAs have their own preferences with respect to data requirements, formats and procedures. These result in the inconsistent application of requirements to CTAs whereby some requirements are applied to one CTA but those same requirements are not applied to other CTAs. In addition, we have also noticed that agreements reached at the EU level (e.g. on a new guideline) are not always (nor rapidly) adopted by individual reviewers.

KEY ISSUE N°3: <u>Regulatory framework not always adapted to the practical requirement</u>

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

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[1] *Verordnung über die Anwendung der Guten Klinischen Praxis bei der Durchführung von klinischen Prüfungen mit Arzneimitteln zur Anwendung am Menschen*

[2] *Arzneimittelgesetz*

[3] *Arzneimittel- und Wirkstoffherstellungsverordnung*

In addition to the examples provided by the EC Public Consultation paper outlining where the EU clinical trials legislation does not adapt to the risk associated with the trial, additional examples include:

- Requirements outlined in the guidance on what constitutes a non-investigational medicinal product, as referred to above.
- The level of detail the guidance expects to be submitted (e.g. expecting a full IMPD for a non-IMP that is approved and marketed in a third country) exceeds the detail necessary to make a fair assessment of the risk to the subjects in the trial. Much of the detail comprises administrative requirements that are not helpful regarding risk assessments.
- Application of ICH principles to quality aspects of clinical trial material.
  ICH Q3A and B on thresholds for impurities are often applied to clinical trials material for Phase 1 and Phase 2 studies. This is despite the ICH guidance having being agreed for marketed products.
- A procedural example is the case of a temporary halt of the study. The current guidelines are not clear as to what constitutes a temporary halt (i.e. should each "pause" in subject recruitment for e.g. logistical or business reasons be considered a temporary halt?) Depending on the circumstances, we believe that notification of temporary halts may not always be necessary and adds to the bureaucratic burden.

We do not believe that a single solution to a risk-adapted approach can be implemented. As part of the EU Commission's Better Regulation Initiative, there needs to be a greater awareness, discussion and understanding of what constitutes risk-based approaches to clinical trials legislation. There needs to be an understanding, acceptance and encouragement from NCAs for risk-based approaches to managing clinical trials. This is providing that such risk-based approaches are justified and based on scientific decisions.

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

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 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 the problem?

A revision to the guidance alone will not address the problems satisfactorily. Guidelines are not legally binding and are open to differences in interpretation by sponsors, regulators and members of ethics committees. Pfizer's view is that the best way to address these issues is to adopt a Regulation. This new 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.

However, we do recognise that any revision to the EU clinical trial legislation will take time to achieve. Pfizer therefore is supportive of efforts by NCA and the Commission towards further harmonisation and standardisation of clinical trial requirements within the scope of the current legislation and through revisions to the various implementing guidelines and texts. To this end we suggest that the Commission encourages and supports NCA in finding greater opportunities for discussion and communication of learnings from experiences among all stakeholders (in particular among members of NCA that conduct the reviews of CTAs).

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?

We believe that amendments to the Directive may address some of the issues. Changes that are needed are outlined in responses to other questions. They include removing national requirements for CTAs, harmonisation of safety reporting requirements, ensuring CTA requirements adapt to the perceived risk of the trial, clarity and agreement on key definitions.

However, two fundamental problems remain:

1. A Directive is subject to interpretation by Member States and additional national requirements when transposed into national law. Differences in interpretation and requirements lead to an increase in the bureaucratic burden with little/no beneficial impact on subject safety. Ultimately, these impact negatively the competitiveness of the EU as a place to conduct clinical research. We would therefore prefer to see the EU clinical trial legislation set out in a Regulation.
2. It is very difficult to legislate to ensure predictability and consistency for a risk-based approach. There needs to be a common understanding across all stakeholders of what constitutes risk-adjusted requirements. This will require extensive discussion before a change in thinking and approach can be achievable.

Pfizer believes that consistency will only be achieved through the implementation of a harmonized framework, set out in a detailed Regulation.

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

We maintain our belief that the nature/stringency of the requirements and obligations should not be driven by the status/identity of the sponsor. We therefore do not agree with the Commission's proposals for an outright exclusion of 'academic' sponsors from the rules of the Directive. 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 there should be a review of the legislation to identify those provisions of the legislation that cause difficulty for 'academic' sponsors. These provisions should then be considered within the context of impact on the safety of participants in the trial. 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 reviewed.

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

KEY ISSUE N°4: Adaptation to peculiarities in trial participants and trial design

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 safe guarding the safety of the clinical trial participants?

Creating networks on paediatric research is necessary but not sufficient. Increased communication, particularly to parents and the public, would be more helpful than amending the Directive. This is particularly so considering that one of the main problems with paediatric clinical research is the fear that these trials generate for patients and their parents.

The French specific requirements for paediatric clinical research could serve as a good model when designing the future system. In France, the current national law for clinical trials in paediatrics allows for the signature of one single parent/guardian under specified conditions[4].

Consultation item n° 15: Should this issue be addressed? What ways have been found in order to reconcile patients' rights and the peculiarities of emergency clinical trials? Which approach is favourable in view of past experiences?

[4] The conditions are that (i) the study presents only negligible risks and constraints, with no influence on medical care to be provided to the participating minor; (ii) that the study is conducted in conjunction with the care of the patient; and (iii) the other holder of parental authority cannot give his authorisation within the necessary timelines given the methodological requirements for conducting the study in light of its objectives. (Article L. 1122-2 of the French Public Health Code)

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

KEY ISSUE N°5: Ensuring compliance with Good Clinical Practices ("GCP") in clinical trials performed in third countries

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

Pfizer has policies and procedures in place to ensure that all trials sponsored by the company comply with GCP. We also have internal procedures to ensure monitoring of such trials and that a rapid response takes place to address any breaches of GCP during those trials.

In addition, the majority of the trials that we conduct (both within the EU and in third countries) are designed and implemented in such a way that the results can be used to support the marketing authorisations of our products. We continue to support EU legislation that requires data used in regulatory submissions to be generated by trials conducted to GCP.

Pfizer is continuously working to improve informed consent, enhance training and selection process of investigators, partner more effectively with governments, ethics committees and the medical community, and enhance quality at outset of study rather than relying only upon (retrospective) monitoring oversight.

We therefore believe that no further legislative action is needed to address this issue. We would support further discussion to ensure concerns about the GCP compliance of trials conducted in third countries are fully addressed (see further below).

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

Pfizer would be particularly interested in engaging in a dialogue with the Commission to further address this issue.

We agree that all of the options put forth in the proposal could potentially minimise the risk that clinical research in third countries is non-compliant with international standards and safety and ethics. However, before any specific legislative actions are proposed, we strongly encourage that a dialogue between industry, regulators and other stakeholders (such as academics and NGOs) take place to determine the extent to which "self-regulation", as suggested in the consultation paper, could positively change the way in which clinical trials in third countries are being performed.

To elaborate, we feel that between EU-based sponsors alone, there are valuable resources available that would ensure that a high level of patient safety is maintained. With input from regulators, other stakeholders and ex-EU sponsors, we are certain that self-imposed requirements can be introduced to address, in part, the issue of GCP non-compliance in clinical trials in third countries. If, for example, we were to promote the sharing of best practices and subsequently created (through the adoption of codes of conduct) requirements to ensure that such best practices were implemented, there would be a greater assurance that clinical trials performed in third countries were being performed consistently and in accordance with international standards. Some examples of the types of best practices that we would expect to be discussed and developed are:

- the use of an ethics section in every clinical trial protocol;
- Investigator training and certification; and
- Monitor training and certification, in particular, focussing on informed consent.

Furthermore, to promote the concept of consistency among all clinical trials, it would also be possible to establish a common set of scientific, operational and ethical criteria for site selection and to develop model contract provisions between sponsors and study sites, with an emphasis on provisions for key issues related to global trials involving ethical issues, such as expected community and participant benefits for volunteering to participate and investigator publishing rights.

We also encourage, as an initial step, supporting capacity-building in third countries where the regulatory

framework for clinical trials is weak. In the past, industry sponsors have routinely worked with international and local groups to improve standards, oversight, and training, and many such circumstances have lead to incredibly beneficial outcomes. For example, Pfizer has worked with regulators and administrators in India to improve the ethics committee at a hospital where we conduct research, and also with government officials in Suriname to set up the country's first clinical trial ethics council. Last year, Pfizer Korea initiated several training programs on good clinical practice standards with the Ministry for Health, the Korea National Enterprise for Clinical Trials (KoNECT) and clinical trial centres from university hospitals. This training reached over 1,000 investigators and study staff.

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?

Pfizer has no further suggestions to add to this Consultation Item.